Calciphylaxis: Emerging Concepts in Prevention, Diagnosis, and Treatment

William A. Wilmer* and Cynthia M. Magro†

*Division of Nephrology, Department of Internal Medicine and †Division of Dermatopathology, Department of Pathology, Ohio State University College of Medicine and Public Health, Columbus, Ohio

ABSTRACT

Calciphylaxis is a small vessel vasculopathy involving mural calcification with intimal proliferation, fibrosis, and thrombosis. This syndrome occurs predominantly in individuals with renal failure and results in ischemia and necrosis of skin, subcutaneous fat, visceral organs, and skeletal muscle. The syndrome causes significant morbidity in the form of infection, organ failure, and pain. Mortality rates are high. In individuals with renal failure, risk factors for the development of calciphylaxis include female sex, Caucasian race, obesity, and diabetes mellitus. Many cases occur within the first year of dialysis treatment. Several recent reports demonstrate that prolonged hyperphosphatemia and/or elevated calcium × phosphorus products are associated with the syndrome. Protein malnutrition increases the likelihood of calciphylaxis, as does warfarin use and hypercoagulable states, such as protein C and/or protein S deficiency. Recent advances in diagnostic tools and therapeutic strategies have helped in the management of patients with calciphylaxis.

Few syndromes encountered in the care of patients with renal disease are as intriguing and poorly understood as calciphylaxis. Although it is an uncommon syndrome, most nephrologists will be confronted with at least one case during their career. Cases of calciphylaxis have been described since the 1960s. The current prevalence of the syndrome has been difficult to chart, and some reports have suggested that from 1% to as high as 4% of the dialysis population may develop some form of calciphylaxis (1).

Calciphylaxis is a vasculopathy confined primarily to patients with renal insufficiency. It causes a spectrum of end-organ damage due to ischemia. The ischemia may be so severe that frank infarction of downstream tissue develops. The most common, and most noticeable, damage is of skin and subcutaneous tissues (Fig. 1). In the skin and subcutaneous fat, the ischemia leads to subcutaneous nodules of infarction and necrotizing skin ulcers that heal poorly and are at risk for infections. Vascular regions with thicker subcutaneous adipose tissue, such as the breast, abdomen, and thighs, are the most common sites of involvement. An acral distribution of ischemic lesions has also been described.

The syndrome is associated with a poor prognosis, perhaps because the vasculopathy is extensive, and in most cases irreversible, when clinical signs are first apparent. The poor prognosis exists despite advancements in dialysis technology. Within weeks of the diagnosis of calciphylaxis it is common for a patient to have significant infectious morbidity. Death within months of the diagnosis is common and often due to sepsis or even visceral organ involvement by the vasculopathy.

Histology of Calciphylaxis

The pathology can be separated into that involving the vasculature and that resulting from the vascular lesions, namely the ischemic pathology distal to the affected vessels. In calciphylaxis, mural calcific and fibrous expansion involves capillaries, venules, arterioles, and small arteries of the dermis and subcutaneous fat, hence defining a calcific thrombogenic microangiopathy (Fig. 2) (2). The diameter of the affected vessels ranges from 30 to 600 μm, with the average size being approximately 100 μm.

Most reports describing calciphylaxis emphasize the medial wall calcification common in many cases. Calcification of the arteriole medial wall is common, but not all cases of calciphylaxis, especially in patients without renal failure, show prominent medial calcification. The most characteristic lesion is one of intimal proliferation and endovascular fibrosis with calcification (2, 3). Calcification precedes the endovascular fibrosis and a complete spectrum of histologic changes is observed. A giant cell reaction may be observed in some vessels (3, 4). The giant cells are usually apposed to the calcifications. Endovascular thrombosis of capillaries and venules may

Address correspondence to: William A. Wilmer, MD, N210 Means Hall, 1654 Upham Dr., Columbus, OH 43210, or e-mail: wilmer.1@osu.edu.

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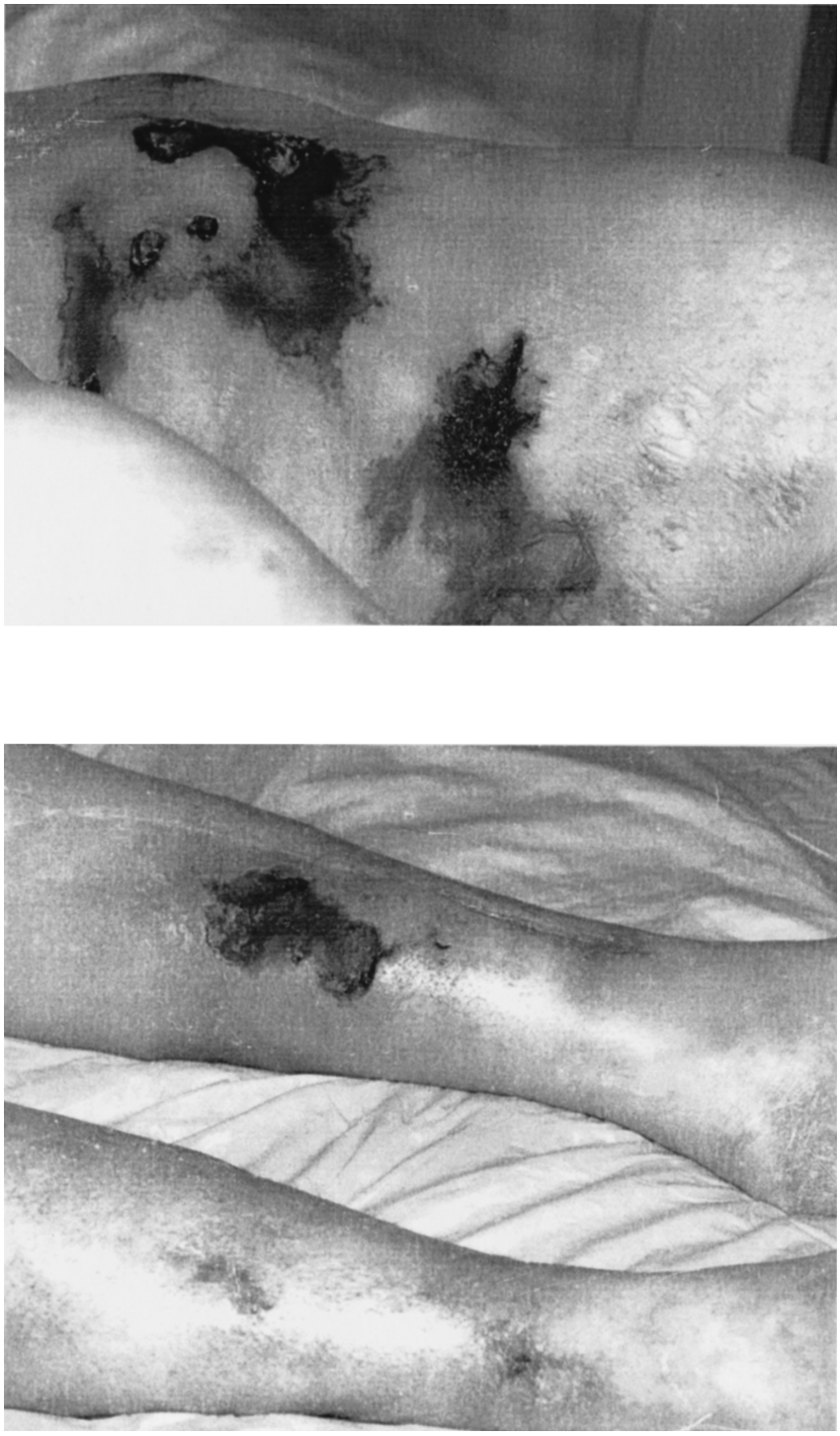

FIG. 1. Skin lesions of two patients with calciphylaxis. The upper panel shows the medial left thigh of an obese, diabetic Caucasian woman with calciphylaxis. This patient was receiving hemodialysis therapy for several years prior to the eruption of these lesions. Several areas of skin mottling and eschar formation are present. The lower panel demonstrates a calf ulcer with overlying eschar of a male hemodialysis patient.

occur and may be an important clue to an underlying procoagulant state. Although thrombosis near the areas of calcification is often present, thrombosis is not a necessary finding for the diagnosis of calciphylaxis or for the development of the tissue ischemia downstream of the vasculopathy.

Although calciphylaxis is a form of vascular calcification, vascular calcification per se should not be equated with calciphylaxis, and it is more appropriate to consider calciphylaxis as an obliterative vasculopathy resulting from intimal changes of the small vessels rather than vessel lumen narrowing as a consequence of medial calcification. It is inaccurate to consider calciphylaxis as a small vessel variant of Mönckeberg's calcification, a medial wall calcification of medium-sized and larger vessels first noted in 1903 and described in diabetic patients, patients with renal failure, as well as those with vitamin D intoxication (5). Mönckeberg's calcification is an innocuous form of dystrophic calcification affecting the media of small and medium arteries. Such calcific medial sclerosis can often be observed within vessels of patients with renal failure who do not have calciphylaxis.

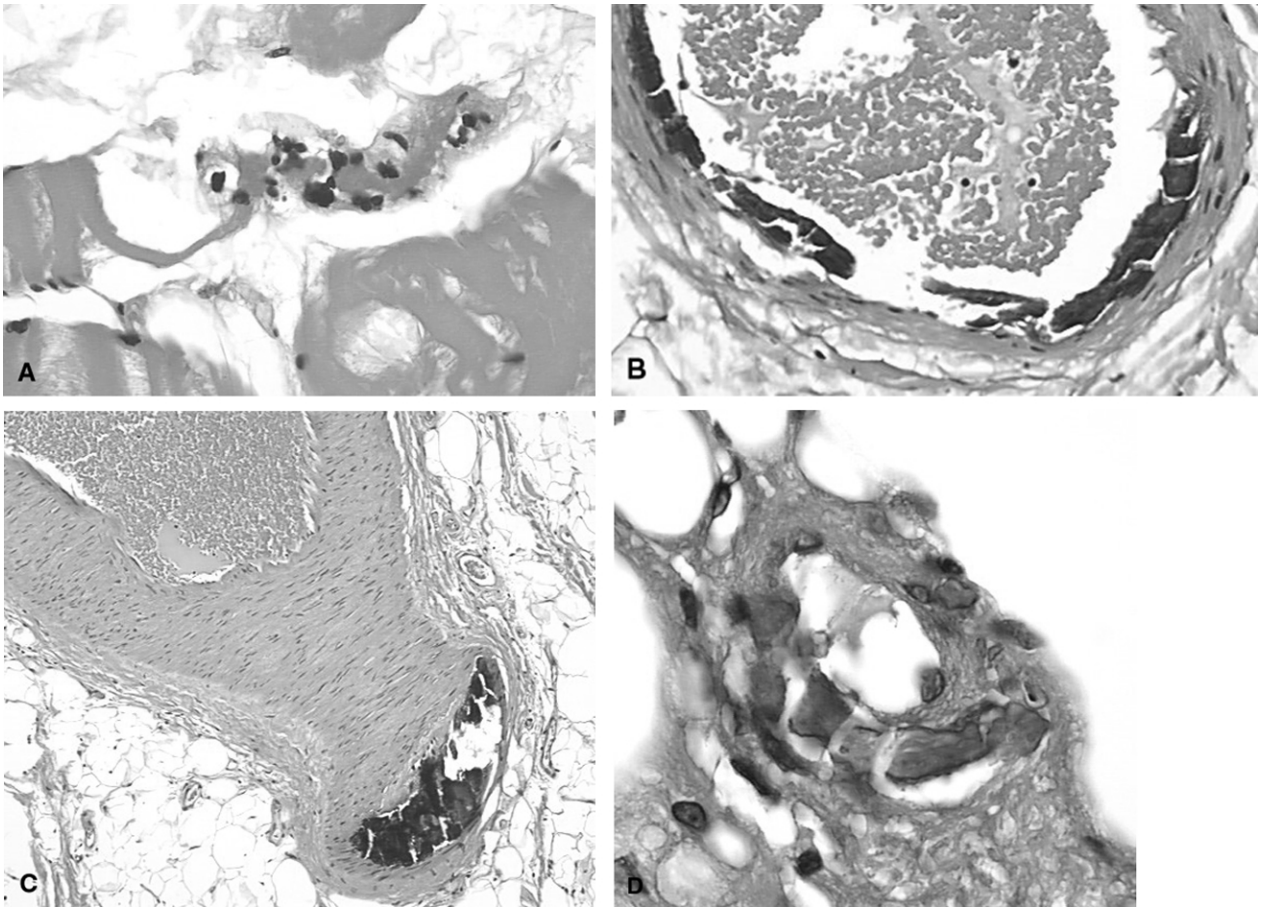

FIG. 2. Calciphylaxis is associated with ischemic complications that can either be insidious in presentation or comprise a dramatic clinical picture of severe cutaneous necrosis (A) Marked muscle atrophy accompanies the vascular calcification identified by von Kassa staining of an affected arteriole. This patient presented with a severe lower extremity myopathy. (B) Calciphylaxis characteristically affects muscular arteries and is characterized by an obliterative intimal calcific process which leads ultimately to luminal ablation. In this view, striking intimal calcification is observed, although without compromise of the vascular lumen. (C) Mönckeberg's medial wall calcific sclerosis. The calcification of the vessel is within the medial wall. The diagnostic intimal changes of calciphylaxis should not be confused with this relatively common lesion. (D) Calciphylaxis also affects small caliber vessels, namely capillaries and venules. In this view there is concentric calcification of the wall of a venule. Such vasculopathy frequently has a concomitant intraluminal fibrin thrombus, possibly reflective of the procoagulant state also thought to be of pathogenetic importance to lesion propagation.

In general, calcific medial sclerosis affects larger vessels; there is no endovascular fibroplasia, giant cell reaction, or associated ischemia. Calciphylaxis, in contrast, is a rare event occurring in the unique milieu of prior vascular sensitization followed by an external stimulus such as trauma, which alters connective tissue fibers, resulting in calcium precipitation.

Since the vasculopathy involves calcification, a significant amount of attention has been given to elevated serum calcium, elevated serum phosphorus, and elevated serum × calcium products ($Ca^{2+} \times PO_4$) in the development of calciphylaxis. In this context investigators have inferred that calciphylaxis may be a form of "metastatic" calcification, which is defined as calcification of normal tissue due to an elevated $Ca^{2+} \times PO_4$ (6). "Dystrophic" calcification, which represents calcification of injured tissue in the setting of a normal serum $Ca^{2+} \times PO_4$ may also occur in the vessels and other tissues of patients with the syndrome. It may be appropriate to consider the calcium deposition of the intima, especially in and around collagen fibrils, to represent a dystrophic calcification that follows vascular damage. A similar form of dystrophic calcification occurs distal to damaged vessels, where subcutaneous fat, muscles, and other organs become calcified following ischemic injury. Both small vessel calcifications and calcific medial sclerosis share a resistance to dissolution after lowering the calcium-phosphate product.

Origin of the Term Calciphylaxis

Tissue calcification in end-stage renal disease (ESRD) was first noted in the 1960s when patients receiving dialysis therapy developed panniculitis with calcified subcutaneous nodules (7,8). In the early 1960s, a series of experiments in nonuremic animals by Selye et al. investigated mechanisms of pathologic organ calcification, and it was speculated that similar mechanisms occurred in uremic humans. Selye et al. first sensitized rodents with dehydrotachysterol, ergocalciferol, or parathyroid hormone and subsequently challenged them

with intravenous iron, intraperitoneal injections of iron, or intraperitoneal administration of egg albumin. These agents generally induced an inflammatory reaction that days later resulted in calcification. Such a "sensitization" stage followed by a "challenge" stage was thought to be the steps of this visceral organ calcification (9–13). It was postulated that such an "anaphylactic" inflammation followed by deposition of calcium was a process that occurred in dialysis patients. Selye et al. also performed studies demonstrating dystrophic calcification of skin injured by repeated forceps pressure. Similarly, dystrophic calcification has been documented downstream of ischemic vascular beds within the subcutaneous tissue of calciphylaxis patients. For example, subcutaneous fat infarction and resultant hemorrhage can lead to firm subcutaneous nodules that are often felt on examination of calciphylaxis patients (14).

The tissue calcification described by Selye et al., as well as the clinical syndrome we know as calciphylaxis, is not an IgE-mediated process, and the term "calciphylaxis" has understandably been considered as inaccurate. Several other descriptive terms have subsequently been advanced for the syndrome. Given the predominance of arteriole involvement, "calcific uremic arteriolopathy" (CUA) is considered a more appropriate term than calciphylaxis (15). Even this term may not totally describe the syndrome since venules may be involved by the calcification, and the term CUA implies that the vasculopathy is a uremic manifestation, when in reality patients may not have any other accepted uremic signs or symptoms. Calcific azotemic arteriolopathy has also been coined to describe the syndrome, and there are several other descriptive terms in the literature—"calcifying panniculitis," "metastatic calcinosis cutas," "cutaneous gangrene with vascular calcification"—that describe this entity (reviewed in ref. 14).

Clinical Presentations of Calciphylaxis

Calciphylaxis occurs predominantly in patients with renal disease, although reports describe the syndrome in patients with cancer (16–18), inflammatory bowel disease (19), and primary hyperparathyroidism with normal kidney function (20,21). These reports of calciphylaxis in patients with normal kidney function suggest the term CUA may be inaccurate.

Despite these reports, the majority of patients with calciphylaxis have kidney disease, the majority of whom are receiving dialysis therapy. Several of the earliest reports suggested that those patients receiving dialysis for more than 1 year are at risk for this syndrome. A similar observation has been made for the risk of coronary calcifications in ESRD patients receiving dialysis for more than 1 year (22). Patients need not have ESRD for years prior to the development of calciphylaxis, however. In our description of 21 calciphylaxis patients followed at Ohio State University, the mean duration of dialysis was 19 ± 17 months (23). We and others have noted that this syndrome occurs in patients with renal insufficiency not yet requiring dialysis (24–26) as well as in patients with renal transplants and minimal renal insufficiency (27–30).

Most patients with calciphylaxis will be diagnosed with skin manifestations. Several excellent descriptions of the dermatologic findings of calciphylaxis have been published over the years (4,14,31–33). The skin manifestations can occur as a solitary skin lesion or multiple lesions covering several body regions. Often there is a relatively rapid evolution of the skin lesions. Patients may first note redness and tenderness of a small localized area. Palor or ecchymosis may surround the redness. A broad violaceous pattern may occur in a livedo reticularis pattern. The initial slight redness may evolve into intense erythema and then frank necrosis with eschar formation. Gangrenous infection may thereafter develop at the site (34). Subcutaneous nodules, often extending centimeters away from any visible skin lesions, can often be felt.

Most of the skin involvement overlies areas of thick adipose tissue. Abdominal and thigh lesions are therefore more common than acral locations (35). If bilateral lesions are present, they are often in a symmetrical, "kissing" pattern where the medial aspects of the extremities are in contact. Patients may present with calf involvement without thigh lesions, and this distal form of calciphylaxis may portend a better prognosis (36). The breasts are another area of involvement (37–39). One report described breast infarction after internal mammary artery harvest for coronary revascularization in a patient without other breast or chest manifestations of calciphylaxis (40).

Although calciphylaxis is most known as a syndrome causing skin ulcers and necrosis, skeletal muscle myopathy has been described. Large muscle groups of the buttocks and thighs appear to be most affected, but smaller muscle groups, such as the tongue, can also develop ischemic lesions (41). The myopathy typically involves painful necrosis of the affected muscle group (42–44) and severe rhabdomyolysis has been reported (42,43). The myopathy may resemble dermatomyositis, but pain, which is less common in true dermatomyositis, is usually present with calciphylaxis (45). Whether due to a coalescence of subcutaneous nodules or to muscle calcification, it is our experience that patients with thigh and buttock myopathy often have a "woody" feel to the muscle groups. In addition, we have noted a variant of calciphylaxis myopathy that includes nonpainful thigh and buttock involvement that results in a gradual loss of lower extremity function (unpublished observation). Histologically this entity is associated with myocyte replacement by fibrosis, leading to the possibility that the "woody" feeling is due predominantly to collagenous replacement of the muscle groups. We have observed patients with this unique presentation who did not have obvious skin lesions overlying the involved muscle groups. The absence of skin findings has been noted in the painful variety of myopathy as well (44).

Heart muscle has also been described as a site of calciphylaxis involvement (46,47). Other unique presentations include arthropathy, necrosis of the penis (48–52), and visceral organ involvement, such as pulmonary calciphylaxis (53,54) and pancreatitis (55). Intestinal ischemia has been described as the cause of death in rare reports (56,57). A unique ocular form of the syndrome has also been described (58). Calciphylaxis also coexists

with large vessel and heart valve calcification (59,60). As outlined below, the mechanisms of calciphylaxis development and of ectopic calcification of large vessels and cardiac valves may be similar. In that context, ectopic peritoneal calcification has also been described in patients with classic calciphylaxis skin lesions (61).

The vasculopathy also causes intense cutaneous pain, which is perhaps the most debilitating aspect of the syndrome (62). This hyperesthesia may be a sentinel symptom for many patients. The pain is often refractory to standard analgesic therapies and often requires aggressive pain management approaches (63).

Because the vasculopathy exists prior to the development of obvious skin lesions or the onset of pain, some inciting event or events apparently worsen the tissue ischemia. Because the medial aspects of thighs and calves are often the site of lesions, local skin trauma is considered a causative factor in the development of lesions (14,64). Similarly an abrupt development of skin ulcers has been described in dialysis patients following postoperative hypotension or associated with sepsis (33,65). Therefore systemic hypotension is a risk for the development of skin lesions and pain in some patients.

Calciphylaxis was first identified in older dialysis patients (66), but recent reports suggest that younger patients are at risk and a few pediatric cases have been described (67). Calciphylaxis occurs more frequently in females (31,68) and in individuals with diabetes (56,69).

Although many of the patients first described with calciphylaxis were receiving hemodialysis rather than peritoneal dialysis, there appears not to be an established dialysis modality that confers protection against this syndrome. Although the syndrome has been described in patients of several different racial backgrounds, Caucasians appear to be more affected (23,68,70). Two recent reports suggest that ESRD patients with human immunodeficiency virus (HIV) viremia may be predisposed to this entity (71,72).

In addition to the demographic risk factors described above, several authors, following Selye et al.'s experimental model, have looked for alterations in blood chemistries or medication exposures to determine what may have precipitated calciphylaxis vasculopathy (8,73,74). Risk factors for the development of calciphylaxis include corticosteroid use and exposure to high doses of iron salts (75). In this manner it is thought that these agents may be challengers to already presensitized vascular beds. A recent report described a patient with systemic lupus erythematosus (SLE) receiving peritoneal dialysis for ESRD who demonstrated cutaneous lesions 2 days after ultraviolet (UV) phototherapy for pruritus (76). Such reports do indeed suggest that calciphylaxis may progress in a manner similar to Selye et al.'s experimental models. Given these reports, it may be inappropriate to dismiss Selye et al.'s line of thinking when investigating the pathogenesis of this vasculopathy.

Risk Factors for the Development of Calciphylaxis

The difficulty in identifying risk factors for the development of calciphylaxis is the uncommon nature of the syndrome. A complete explanation of why calciphylaxis develops in some patients but not others is complicated by the retrospective nature of most reports that describe fewer than 20 cases. Despite this limitation, several reports list the same risk factors for the syndrome. Some of the more frequently listed risk factors and a review of their potential pathogenic roles are as follows.

The Role of Obesity and Increased Adipose Mass in the Development of Calciphylaxis

Obesity is a risk factor for calciphylaxis and obesity may be the reason that diabetes mellitus, particularly type 2 diabetes mellitus, is also a risk factor for the syndrome. Bleyer et al. (77) noted that the average body mass index (BMI) of nine calciphylaxis patients followed by his group exceeded 30 kg/m^2, a value much higher than that of other dialysis patients who did not develop calciphylaxis. These authors suggested that for every BMI increase of 1 kg/m^2, the odds ratio of developing calciphylaxis was 6.29 [95% confidence interval (CI) 3.7–10.7]. An elevated BMI was confirmed as a risk factor in 19 patients with calciphylaxis described by Mazhar et al. (68). We reported that the weight of 21 patients with calciphylaxis, the majority of whom were women, was 94 $\pm$ 26 kg (mean $\pm$ SD) at the time of diagnosis (23).

No hypothesis has adequately explained why obese, diabetic Caucasian women are more likely to develop calciphylaxis compared to other patients with renal failure. It is noteworthy that the cutaneous lesions of calciphylaxis occur in areas of greatest subcutaneous adipose thickness. Often the skin breakdown in these subcutaneous tissues occurs near areas of local and likely repeated trauma. Summers et al. (78) have shown that abdominal adipose tissue has a diminished blood flow in obese patients (i.e., those with BMI $> 30\ kg/m^2$) relative to nonobese individuals. Perhaps this is due to gravity-mediated tension of a large panniculitis that causes partial occlusion of adipose vessels. Therefore obese patients, particularly those patients with central obesity, may have poorer "baseline" blood flow at the abdomen, buttocks, and upper thighs. This lower blood flow may worsen to a pathologically low level if vascular calcification occurs. This scenario has been forwarded as a possible mechanism in the development of calciphylaxis skin lesions (14).

The Role of Elevated Serum Calcium and/or Phosphorus and/or Calcium $\times$ Phosphorus Product in the Development of Calciphylaxis

Much attention has focused on the role of elevated serum calcium and serum phosphorus levels in patients with renal failure (15,79). This attention is understandable as studies have demonstrated that an elevated $Ca^{2+} \times PO_4$ is associated with elevated rates of mortality, much of it due to vascular disease (80). In a review of national dialysis data, it was calculated that 39% of dialysis patients had a $Ca^{2+} \times PO_4 > 72\ mg^2/dl^2$, and that the relative mortality risk was 1.34 in those patients with a $Ca^{2+} \times PO_4$ of 73–132 mg^2/dl^2 (81). Although

this is a broad range of $Ca^{2+} \times PO_4$, the concern that vascular calcification increases because of an elevated $Ca^{2+} \times PO_4$ appears warranted. In this context it can be argued that calciphylaxis may simply represent a form of metastatic vascular calcification. Although the pathologic role of medial calcification may be minimal, observations that intimal calcifications exist in many lesions suggest that altered calcium and phosphorus balance may be detrimental. Some of the intimal calcifications occur near and in collagen deposition, suggesting that either a metastatic and/or dystrophic calcification process has occurred.

In the context of calciphylaxis, earlier reports on the role of elevated calcium or phosphorus concentrations were mixed. Compared to other patients with ESRD, patients with calciphylaxis may not have statistically different serum calcium or phosphorus levels at the time the diagnosis is made (72,77). For example, in our review of 21 patients, serum $Ca^{2+} \times PO_4$ were not elevated above those of a control group of dialysis patients without calciphylaxis (23). This lack of association may be incorrect, given the manner in which serum chemistry values are compared. Many studies, including ours, have looked at calcium and phosphorus values at the time of presentation. However, patients with calciphylaxis may have pain, infections, and ischemic tissue injury that interfere with appetite and lower dietary intake. It is well established that lower protein intake in ESRD patients lowers serum phosphorus levels as well as serum parathyroid hormone (PTH) levels (82).

Therefore time-averaged elevations in serum calcium, phosphorus, and $Ca^{2+} \times PO_4$ may be more indicative of the risk for calciphylaxis. For example, an intriguing case of a patient without kidney disease who developed calciphylaxis skin lesions due to total parenteral nutrition (TPN)-associated hyperphosphatemia suggests that prolonged elevation of serum phosphorus levels may be pathologic (83). By looking more closely at time-averaged values, recent studies have shown calciphylaxis is indeed associated with hyperphosphatemia (68,70). These more recent reports support an earlier one by Gipstein et al. (30) who described 11 calciphylaxis patients who were quite hyperphosphatemic.

The difficulty in the clinical interpretation of these recent studies is that most of the calciphylaxis patients had phosphorus and $Ca^{2+} \times PO_4$ values that overlapped with those of patients without calciphylaxis. Furthermore, the abnormalities in the blood chemistries were not severe in the historical context of ESRD care. In Ahmed et al.'s (70) report, 6 of 10 calciphylaxis patients had 6-month average serum phosphorus values greater than 7 mg/dl, but 3 of the 10 had average phosphorus values less than 6 mg/dl. Seven of these 10 calciphylaxis patients had time-averaged $Ca^{2+} \times PO_4 < 70$ mg^2/dl^2; the $Ca^{2+} \times PO_4$ of 180 control patients without the syndrome was 50 ± 17 mg^2/dl^2. Hyperphosphatemia was also identified as a risk factor in 19 calciphylaxis patients described by Mazhar et al. (68) (mean phosphorus at the time of diagnosis of 6.2 ± 1.8 mg/dl). This may have been statistically significant due to the low phosphorus values of the control group (4.9 ± 1.7 mg/dl) (68). In that study, the mean $Ca^{2+} \times PO_4$ of the 19 control patients was less than 61 mg^2/dl^2. These observations highlight two important points. First, since these reports acknowledge a statistically significant risk of elevated time-average hyperphosphatemia and $Ca^{2+} \times PO_4$, redefining the targets of calcium, phosphorus, and $Ca^{2+} \times PO_4$ in renal failure patients seems prudent (80). Second, since calciphylaxis patients may demonstrate a level of phosphorus control similar to patients without calciphylaxis, other etiologic factors for the development of vascular lesions must exist.

Although phosphorus appears to be the main ion to control, hypercalcemia is also causative in vascular calcification. The ability of a hypercalcemic milieu to result in calciphylaxis was demonstrated by Khafif et al. (84) in a report of a patient with hypercalcemia due to primary hyperparathyroidism who rapidly developed calciphylaxis skin lesions. Similarly a risk for the development of calciphylaxis was reported in ESRD patients using large doses of calcium salts as dietary phosphate binders (85,86). A similar observation that calcium ingestion correlates with more generalized forms of vascular calcification has been made (87). Despite these reports, in Ahmed et al.'s (70) and Mazhar et al.'s (68) studies the time-averaged serum calcium levels were no different in calciphylaxis patients than in control populations.

How does an elevated calcium or phosphorus level cause vessel damage? The biology of vascular calcification is the focus of intense study (88,89), especially in patients with kidney disease (90,91). As outlined previously, vascular calcification is only one aspect of calciphylaxis and it appears that the degree of intimal changes within affected vessels corresponds better with the obliterative nature of the syndrome. Fisher and Morris (3) suggested that the calcium deposition in calciphylaxis resembled an endovascular form of pseudogout with an associated inflammatory reaction.

Since medial and even intimal calcifications are noted in many vessels, lessons pertinent to calciphylaxis may be gleaned from recent experimental studies involving larger vessel calcification (92,93). Vascular calcification commonly occurs in patients with renal disease. Several interesting reports suggest vascular calcification may occur early in the development of most forms of kidney disease. Diabetic patients with microalbuminuria, for example, are more likely to have radiographically apparent vascular calcification than diabetics without albuminuria (94). The commonality of the process makes the role of medial wall calcification in the pathogenesis of calciphylaxis difficult to interpret.

Such vascular calcification in renal disease appears to be a regulated biologic process. The medial wall calcification is associated with, and perhaps requires, an altered vascular smooth muscle cell (SMC) phenotype (89,95). Involved in this process is an imbalance between local vascular promoters and inhibitors of the calcification process (91,96,97). The thought that vascular calcification is a regulated process is consistent with the observations that the media and not other sections of a vessel wall are calcified in most forms of vascular calcification. This appears true for a variety of vascular

injuries that are associated with calcium deposition. For example, in an animal model of intimal damage induced by balloon angioplasty, hypercalcemia induces medial, not intimal, calcification (98).

The following observations further support the concept of a regulated process in vascular calcification, including the intimal changes noted in calciphylaxis. First, it is noteworthy that bone, tooth mineral, and ectopic foci of calcification actually exist in disequilibrium with blood gradients of calcium and phosphorus (reviewed in ref. 99). Nucleators of calcium crystal formation must be present for vessel calcification to occur. Second, matrices that calcify within a vascular wall often are collagenous; however, collagen fibril calcification does not occur when collagen matrix is placed in a high-calcium or phosphorus solution unless a nucleator is also present. The steps of such ectopic calcification include the initial appearance of intramitochondrial granules of mineral within connective tissue cells, followed by the appearance of extracellular matrix vesicles, and thereafter the construction of mineral crystals (100). Matrix vesicle calcification has been shown by electron microscopy to occur in calciphylaxis lesions (70). Third, mature atherosclerotic lesions and calcifications of native cardiac valves and xenograft valves occur in a pattern similar to primitive bone formation (101,102). Furthermore, in atherosclerotic lesions, it is common for intimal calcification to be present, but often at sites where macrophage-derived foam cells and migrated smooth muscle cells have advanced to the intima.

The regulation of vascular calcification involves a phenotypic change of vascular smooth muscle cells, and potentially other cells of the vessel. Vascular cells can be induced to express those genes and proteins that are expressed by osteoblasts when osteoid is secreted. The role of such a phenotypic shift has been thoroughly reviewed by Davies and Hruska (91). Elevated phosphorus values have recently been implicated in such a phenotypic shift. In an intriguing series of studies, Jono et al. (95) recently showed that cultured human vascular smooth muscle cells calcify their surrounding media when exposed to excessive inorganic phosphorus levels. The increased mineralization of the smooth muscle cell media induced by the high phosphorus concentration was associated with osteocalcin expression. Osteocalcin, a protein first noted in osteoblasts, is believed to promote tissue calcium deposition. Osteocalcin up-regulation by phosphorus is one of the first reports linking elevated serum phosphorus and the calcification that occurs in ESRD patients.

Other stimulators of vascular calcification have been identified. Osteopontin is a phosphoric-like protein that adheres to major proteins during the mineralization process. It has been isolated in several types of calcifying tissue (70,103) and is expressed by smooth muscle cell derivatives present in atherosclerotic plaques (104). Similar to osteocalcin, osteopontin is stimulated by high-phosphorus environments (105). Ahmed et al. (70) recently showed that arterioles from calciphylaxis patients demonstrated osteopontin protein deposition, but only in regions that stained for calcium deposition.

Inhibitors of vascular calcification have also been described. Therefore it is plausible that vascular calcification occurs due to an imbalance of calcification promoters and inhibitors. Inhibitors of calcification include osteoprotegerin and matrix GLA protein (MGP). MGP was originally thought to be involved in the promotion of calcification, since MGP protein as well as genomic expression of MGP is elevated at the borders of calcifying tissue (106–108). However, MGP appears to be constitutively expressed by smooth muscle cells and in macrophages adherent to intimal injury (108–110) and recent clinical observations and experimental studies suggest MGP actually inhibits calcification. MGP levels are extremely elevated in cartilaginous tissue and elevated MGP is believed to inhibit cartilaginous calcification (111,112). Keutel syndrome is a very rare human genetic disease in which nonfunctioning MGP causes costal, tracheal, and nasal growth plate cartilage calcification in growing children, resulting in facial and other cartilage abnormalities (113–116). MGP knockout mice develop an aggressive form of vascular calcification and often die a hemorrhagic death due to spontaneous aortic fracture. Although these reports argue that MGP inhibits vascular calcium deposition, of interest is that individuals with Keutel syndrome do not demonstrate florid vascular disease (116). Therefore the role of MGP or other inhibitors of ectopic calcification is not firmly established for vascular calcification in general or for calciphylaxis specifically.

The Role of Warfarin Use in the Development of Calciphylaxis

Warfarin may be able to alter the balance of calcification promoters and inhibitors. Experimental rat models demonstrate that warfarin therapy precipitates arteriole and cardiac valve calcification (117). Work by Price et al. (117) has attempted to illustrate some of the mechanisms of this observation. One thought is that arteriole calcification occurs due to inhibition of MGP function within vascular walls, even when MGP levels are "normal." MGP requires γ-carboxylation for its functional activity (109) and warfarin, through its inhibition of γ-carboxylation, can inhibit MGP function. Due to inefficient uptake of vitamin K by smooth muscle cells, as compared to hepatocytes, the inhibition of MGP γ-carboxylation by warfarin cannot be totally restored by concomitant vitamin K therapy (118). In studies in which rats are simultaneously given warfarin and vitamin K replacement, arteriole calcification and cardiac valve calcification progresses, leading eventually to death (117). The role of inhibited or impaired γ-carboxylation of MGP in the pathogenesis of calciphylaxis vasculopathy is entirely speculative, but other observations (outlined below) suggest there may be some validity to its pathologic role.

The Role of Protein C and/or Protein S Deficiency in Calciphylaxis

Several authors have noted that calciphylaxis lesions develop in locations similar to those of the thrombotic

lesions of warfarin necrosis. This is particularly true of skin lesions overlying areas of excessive adipose tissue. Thrombosis is not a prerequisite for the diagnosis of calciphylaxis, but thrombus formation is frequently observed in calciphylaxis vessels. It is plausible that in many patients, thrombus formation is the event which causes a subclinical syndrome (vasculopathy without skin necrosis) to become clinically apparent (skin necrosis).

It is intriguing that thrombus deposition in calciphylaxis vasculopathy has been described in patients taking warfarin at doses that cause systemic anticoagulation (119,120). Coates et al. (56) noted that 8 of 16 calciphylaxis patients described by their group were receiving warfarin at the time of diagnosis. On biopsy or at autopsy, thrombus was often seen within the calcified vessels despite the patients' use of warfarin (56). The frequency of vessel thrombosis has led some investigators to question if patients with calciphylaxis have hypercoagulability syndromes, such as protein C or protein S deficiencies. Protein C and protein S are vitamin K-dependent inhibitors of thrombus that are antagonized by warfarin, typically prior to antagonism of liver-derived clotting factors.

Low, or low-normal, levels of protein C or protein S antigen have been documented in calciphylaxis patients (121). Those reports which have also reported functional assays for protein C or protein S have suggested that extremely low levels of function exist, even when antigen levels are low-normal (122). The inference of these reports is that the function of protein C and protein S may be additionally depressed, perhaps by warfarin use, in patients with calciphylaxis, despite only slightly diminished protein C and protein S levels.

Opponents of the role of protein C or protein S deficiencies argue that the thrombus formation noted in many calciphylaxis cases does not occur at the site of organ necrosis, and likely represents a consequence of a very low blood flow state. Furthermore, venules are clotted more often than arterioles in protein C or protein S deficiency; in calciphylaxis, arterioles are more often clotted than venules. Also noteworthy are those few calciphylaxis patients who heal their calciphylaxis lesions despite persistently abnormal protein C or protein S assays (123). Therefore the causative role of protein C or protein S abnormalities in calciphylaxis is uncertain.

Is There a Possible Role of Vitamin K Deficiency in the Development of Calciphylaxis?

That functional assays for protein C or protein S are often low in calciphylaxis implies that some patients may have a relative vitamin K deficiency causing a decline in these clotting inhibitors. If so, the procoagulant state that develops in some calciphylaxis patients may be preventable or treatable with vitamin K supplementation. In addition to a procoagulant affect, vitamin K deficiency could theoretically antagonize MGP function and stimulate vascular calcification.

Very little literature exists documenting alterations of vitamin K levels in ESRD patients. One report has suggested that antibiotic therapy can lessen a dialysis patient's level of this lipid soluble vitamin (124). Of interest, Soundararajan et al. (125) reported a case of calciphylaxis skin necrosis and protein C deficiency in a renal failure patient with vitamin K depletion. These authors suggested that vitamin K replacement of this patient stabilized the calciphylaxis lesions. Vitamin K deficiency in calciphylaxis remains a potential area of clinical study. Given the observation that many patients with calciphylaxis are quite ill and have received multiple courses of broad-spectrum antibiotics months before presentation, a relative vitamin K deficiency may explain some aspects of calciphylaxis development.

The Role of Protein Malnutrition in the Development of Calciphylaxis

Bleyer et al. (77) showed a very strong association of a low serum albumin level and the development of calciphylaxis. In this study, serum albumin levels in the 2 g/dl range were associated with a dramatically heightened risk of calciphylaxis (77). The cause and effect of this was not clear and it is entirely conceivable that the patients' low serum albumin values were due to a diminished nutritional intake, systemic inflammation, and serious infections that antagonized hepatic synthesis of albumin within weeks of the diagnosis. Mazhar et al. (68), in a case-controlled, retrospective review of 19 calciphylaxis patients, also demonstrated a statistically significant risk of low serum albumin values prior to the development of calciphylaxis.

There may indeed be a causative role of malnutrition in the development of calciphylaxis. The association of malnutrition in atherosclerotic and cardiac valve disease is now firmly established (126,127) and it is known that vascular disease other than calciphylaxis occurs more frequently in ESRD patients who are malnourished (128). In a similar manner, Wang et al. (127) recently determined that cardiac valve calcification in ESRD patients occurs more frequently in the setting of protein malnutrition, even when serum calcium, phosphorus, and $Ca^{2+} \times PO_4$ are normal. In Wang et al.'s study, the degree of malnutrition (the degree of serum albumin decrease) predicted an increasingly greater risk of valve calcification.

The Role of PTH in the Development of Calciphylaxis

The 1968 report of calcifying panniculitis in a patient with renal failure attributed the lesions to secondary hyperparathyroidism (7). As will be described later, parathyroidectomy has for many clinicians been the mainstay of treatment for calciphylaxis. These concerns about PTH refer to those original thoughts that calciphylaxis developed in a manner similar to the animal models of Selye et al., where a "sensitizer" promoted calcification when a "challenger" agent was also present. In Selye et al.'s studies, rodents were treated with PTH as a "sensitizing" agent.

In most reported cases of calciphylaxis, serum PTH values are elevated above acceptable thresholds for ESRD patients (14,33,68,70). For example, the mean

serum intact PTH value in 21 calciphylaxis patients our group recently followed was 440 ± 535 pg/dl (23). Whether PTH causes vascular injury by stimulating an intimal proliferation that eventually obliterates a vascular lumen remains unknown. An obvious role of elevated PTH levels in calciphylaxis is the perturbation of calcium and phosphorus homeostasis that often occurs. Parathyroidectomy may therefore be helpful only by normalizing serum calcium and phosphorus levels. PTH is also a vasoactive compound that causes vasodilation of resistance vessels (129). It is plausible that elevated PTH levels could induce vasodilation of some arterioles and create a vascular "steal" phenomenon in calciphylaxis arterioles that are calcified and unable to autoregulate. Such physiology is more theoretical than proved, but it is possible that the rapid improvement of some calciphylaxis lesions after parathyroid surgery is a hemodynamic effect.

The true role of PTH in the development of calciphylaxis may not be clear because PTH assays currently used in the clinical setting may be inaccurate. The current assays that measure carboxyl-terminal PTH may not be able to assess the truly bioactive forms of the hormone because the assays may cross-react with fragments of PTH that are not biologically active (130). A high PTH by such an assay may not be associated with parathyroid bone disease, and an acceptable value may be associated with a low bone turnover state. A low bone turnover state (low turnover osteomalacia and adynamic bone disease) increases the risk of hyperphosphatemia and hypercalcemia in response to vitamin D analogs and calcium-containing phosphate binders (131). It is intriguing that adynamic bone disease due to suppressed PTH values may be associated with calciphylaxis even when $Ca^{2+} \times PO_4$ is low (132). Because a low bone turnover state may be a risk for calciphylaxis, transitioning patients from calcium-containing phosphate binders to aluminum-containing binders may not be prudent.

The Role of Vitamin D Analogs in the Development of Calciphylaxis

Elevations in vitamin D cause increases in serum calcium concentrations. High serum calcium levels due to high vitamin D levels cause Mönckebergs variant of vascular calcification, described decades ago. Similar to PTH, vitamin D analogs were used as "sensitizers" in Seyle et al.'s model of calciphylaxis.

Some evidence exists that high levels of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] deleteriously affect the vascular smooth cell phenotype and cause medial wall calcification. Recent in vitro studies suggest vitamin D suppresses endogenous inhibitors of SMC calcification to induce ectopic calcium deposition (133). Other reports demonstrate that vitamin D stimulates SMC expression of alkaline phosphatase which thereafter stimulates vascular calcification (133). In contrast, other reports suggest vitamin D_3 stimulates MGP expression (108), which if biologically active would be expected to inhibit calcification.

Little is known of the risk of using higher than average doses of vitamin D_3 to suppress elevated serum PTH values. Keeping a serum PTH level in an acceptable range but using massive doses of calcitriol may be more deleterious that the effects of a higher PTH value but lower calcitriol dose. A composite risk score using time-averaged PTH values and calcitriol doses may be insightful concerning the development of calciphylaxis, but this area remains unstudied at present.

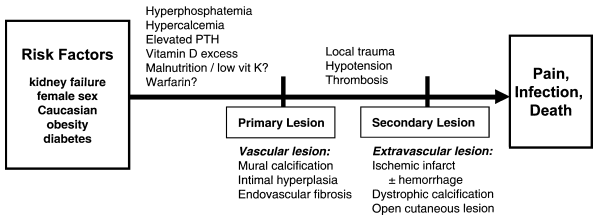

FIG. 3. The development of calciphylaxis organ damage can be considered a two-step process involving first a vascular injury and then injury of tissue distal to the vessel.

As discussed above, Malluche et al. (131) have recently expressed caution that the use of vitamin D analogs and overcontrol of PTH values can cause low bone turnover, leading to hyperphosphatemia and hypercalcemia. Fournier (134) has recently suggested that the risk of calcium salt use in calciphylaxis described by Guerin et al. (87) may be related to the concomitant use of vitamin D analogs, especially in patients with adynamic bone disease.

The Diagnosis of Calciphylaxis

The development of calciphylaxis can be considered a two-stage process: the development of the vascular lesion and the development of tissue ischemia due to the vascular lesion, plus other clinical events (14). Fig. 3 outlines how a two-step injury may occur in the development of calciphylaxis. This figure highlights the difficulty in diagnosing calciphylaxis. By the time the clinical entity is apparent, it is often too late to reverse the vasculopathy. Also it is often too late to improve the morbidity and mortality of the syndrome. The diagnostic tests—and their pitfalls—currently used to identify the presence of calciphylaxis are as follows.

Physical Examination

Many clinicians base the diagnosis of calciphylaxis solely on physical examination findings. As outlined above, the traditional diagnosis of calciphylaxis occurs when patients with chronic renal failure or ESRD present with subcutaneous and cutaneous findings of nodules, firmness of the skin, livedo reticularis, palor, redness, necrotic lesions, and eschars with varying degrees of hyperesthesia of the skin. Other vascular diseases may cause a similar presentation and should be ruled out when using this diagnostic approach.

Exclusion of Other Vascular Diseases That Cause Calciphylaxis-Like Lesions

Other diseases may cause skin lesions that resemble calciphylaxis, and a short differential list should be kept in mind in ESRD patients presenting with "classical"

TABLE 1. Percentage of body regions in control and calciphylaxis patients with room air $TCpo_2$ level 30 mm Hg and/or 100% FiO_2 90 mm Hg

$TCpo_2$ level (mm Hg)	Controls	Calciphylaxis	
		Body regions with lesions	Body regions without lesions
30 mm Hg while breathing RA	0.8%	62%	26%
90 mm Hg while breathing 100% FiO_2	11%	90%	45%
30 with RA and 90 with 100% FiO_2	0.8%	68%	24%

skin or other organ involvement. Perhaps the most difficult diagnostic dilemma occurs when a patient with severe peripheral vascular disease (PVD) presents with lower extremity or acral locations of lesions, which are less common of calciphylaxis but typical of PVD (135,136). Atheroemboli to the lower extremities should also be in the differential of distal lesions. In patients with ESRD due to oxaluria, a vasculopathy similar to calciphylaxis, but with intense oxalate deposition in the vasculature, has been described (137).

Cryoprecipitate disorders can also cause occlusion of small vessels, leading to skin lesions that can be confused with calciphylaxis. Cryoglobulinemia may present in ESRD with the classical palpable purpura or with ischemic necrosis of the skin that resembles calciphylaxis (138). Such manifestations of cryoglobulinemia may respond favorably to pheresis therapy. Cryofibrinogenemia, a rare cryoprecipitate disorder associated with elevated serum fibrinogen levels that precipitate in cold, can cause small arteriole occlusion similar to calciphylaxis. Histologically this lesion differs from calciphylaxis by the presence of eosinophilic material that precipitates in affected arterioles, leading to local inflammation. As with cryoglobulinemia, this disease responds to pheresis (139). Necrotizing vasculitides other than cryoprecipitate disorders should also be considered in patients with suspicious skin lesions (140).

Tissue Biopsy

It can also be argued that the diagnosis of calciphylaxis can only be made by a biopsy that shows appropriate calcification of small arterioles or venules. The problem with performing skin biopsies in calciphylaxis is the poor likelihood of healing the biopsy site. The dystrophic calcification at the area of biopsy trauma can become the primary cutaneous lesion that fails to heal and becomes infected. We have tended to perform a biopsy only when a unique area of skin involvement requires the exclusion of disease processes listed above, or when a unique location of the lesion (an acral location, for example) is present. We have also performed biopsies when myopathy exists.

Measurements of Transcutaneous Oxygen Saturation ($TCPO_2$)

$TCPO_2$ probes are capable of identifying skin ischemia quickly and noninvasively. Low $TCPO_2$ levels associated with severe peripheral vascular disease, for example, have historically helped predict the viability of skin grafting or to localize tissue viability in limb amputation. Our group used $TCPO_2$ measurements to define the transcutaneous oxygen saturation of calciphylaxis patients and control patients with kidney disease. We measured $TCPO_2$ levels at the chest, abdomen, and thighs of patients with calciphylaxis after excluding that the low $TCPO_2$ levels could be due to large vessel disease (23). In our studies (Table 1), skin ischemia was generalized and severe in patients with calciphylaxis, even in body regions where skin lesions were absent. We noted that resting room air skin oxygen saturation was generally less than 30 mmHg and skin oxygenation after 100% FIO_2 administration was often less than 90 mmHg in most body regions of calciphylaxis patients. We concluded that it is uncommon to observe this low level of skin oxygenation in control patients. We currently are using these observations, which are limited to proximal forms of calciphylaxis, to help make a diagnosis of calciphylaxis when the physical examination is also suggestive of this syndrome. It is noteworthy that these studies have not been duplicated and may not yield the diagnostic power we suspect. However, there may be some value to using this modality as a screening test that identifies and quantifies skin ischemia (identifies the primary lesions) prior to the eruption of the skin necrosis (secondary lesions).

Bone Scans

In our studies using $TCPO_2$ probes, we described that diffuse and severe skin ischemia exists in calciphylaxis patients. Our results suggest that the vasculopathy of calciphylaxis is quite diffuse and larger than that realized by looking at the location of skin lesions. In a similar line of thought, bone scan imaging has been used as a diagnostic tool to identify the presence of extraosseous calcification (vascular calcification and dystrophic lesions) in patients with physical examination findings consistent with calciphylaxis. The limits of this imaging technique are that it is relatively expensive and not sensitive or specific in identifying calciphylaxis lesions (141). We routinely do not perform this imaging procedure for diagnostic purposes.

Xeroradiography

Xeroradiography identifies extraosseous calcification better than plain film imaging. Using mammogram-grade film, xeroradiography of areas with suspicious skin lesions is often helpful in showing extremely small vessel calcification that is consistent with calciphylaxis. This type of radiography is compromised in abdominal and thigh lesions due to tissue thickness. Xeroradiography also identifies large vessel calcification, such as Mönckeberg's variant of calcification, that occurs commonly in patients with diabetes or renal failure.

Treatment Options

The outcomes for patients with calciphylaxis are universally quite poor. For those patients with skin

necrosis, the ability to heal open wounds and reverse the vasculopathy is limited, and infection of the skin, with the progression to sepsis, is common. The extent of the ischemic pain also requires extremely aggressive analgesic use that disrupts the quality of life for many patients.

The literature is limited in the number of reports of long-term survival of calciphylaxis, or even reports of patients who have healed their skin lesions or myopathy. Undoubtedly nephrologists do identify patients with early clinical evidence of calciphylaxis who, through appropriate medical management, survive many months or years later.

The interventions for patients with calciphylaxis supported by the literature or by our group's clinical experience are summarized as follows.

Preventive Strategies

Calciphylaxis, like vascular calcification in general, should be considered a preventable lesion in patients with chronic renal failure (CRF) or ESRD, despite an incomplete understanding of the mechanisms involved in its development. Attention to calcium, phosphorus, PTH homeostasis, and nutritional parameters likely will prevent many cases of calciphylaxis. Established demographic risk factors of female sex, Caucasian race, obesity, and diabetes should guide nephrologists to redouble their efforts at controlling serum calcium and phosphorus values.

Weight reduction and optimization of nutrition should also be goals for at-risk patients. As discussed above, obesity is associated with decreased abdominal adipose blood flow, which may contribute to development of ischemic lesions earlier in the course of calciphylaxis. Therefore aggressive control of blood sugar and weight reduction seems prudent. Given the strong association of calciphylaxis with diabetes and obesity, it is possible that vascular smooth muscle cell biology is somehow affected by these disorders. Only recently has the role of leptin in smooth muscle cell biology and vascular calcification been investigated (142). Future studies will undoubtedly extend this line of investigation.

Reassess the Dialysis Prescription

It has not been demonstrated that calciphylaxis is associated with a uremic toxin that induces endothelial injury or alters smooth muscle cell biology. Given the uniqueness of this form of vasculopathy to patients with renal dysfunction, the possibility exists that some uremic stimulus of the vascular injury is present and removable by dialysis. Unfortunately there is little literature to support that increasing dialysis efficiency can improve the incidence, morbidity, or mortality of calciphylaxis.

Therefore the association of calciphylaxis with renal failure may simply be due to hyperphosphatemia and/or associated increases in $Ca^{2+} \times PO_4$ that develop in ESRD patients. With this aim in mind, some have advocated use of low-calcium dialysate solutions for peritoneal dialysis and hemodialysis (143). Similarly Llach (144) has suggested dialyzing hemodialysis patients with calciphylaxis against a zero-calcium dialysate bath. The concept that transient episodes of hypocalcemia may not only improve serum $Ca^{2+} \times PO_4$, but also help remove calcium from calcified tissues is interesting but unproven.

Improve Serum Calcium and Phosphorus Levels

As a means of preventing vascular disease in ESRD and pre-ESRD patients, several new target values for serum calcium and phosphorus have been recently proposed by Block and Port (81). These new targets make sense as a way to prevent the development of calciphylaxis as well. Whether the vascular calcification or the dystrophic calcification of injured subcutaneous tissue can improve with control of $Ca^{2+} \times PO_4$, serum phosphorus, and serum calcium to these target values is unknown. They include $Ca^{2+} \times PO_4 < 55\ mg^2/dl^2$, serum phosphorus < 5.5 mg/dl, and serum calcium < 9.6 mg/dl.

Similar to the therapeutic interventions of a zero-calcium bath, other authors have suggested a role of polyphosphates in stimulating bone formation and lowering serum calcium and/or phosphorus, thereby improving cutaneous lesions (145). To our knowledge, no follow-up studies have confirmed this.

The suggestion that use of calcium salts as a phosphate binder should be curtailed or even abandoned may have some merit, if use is excessive (more than 5 g of calcium/day). In patient's at risk for calciphylaxis, it may be worthwhile to convert a patient from oral calcium salts to noncalcium phosphate binders as a means of binding dietary phosphate. However, as outlined thoroughly above, the rate-limiting step for most vascular calcifications including calciphylaxis appears to be hyperphosphatemia as opposed to an elevated serum calcium value, and therapeutic goals of serum phosphorus control may only be met with calcium salt use in some patients.

Rule Out Large-Vessel Atherosclerotic Disease

For calciphylaxis patients with lower extremity involvement, cutaneous lesions can resemble those of severe large-vessel atherosclerotic disease, particularly in patients with diabetes. It is important to investigate the presence of large-vessel disease in limbs affected by calciphylaxis because if PVD is present, it may be worth large-vessel revascularization or angioplasty to establish better flow to the small vessels affected by calciphylaxis. As in most forms of vascular disease, there may be a benefit in correcting anemia as well.

Prevent Subcutaneous Trauma in "At-Risk" Body Regions

In patients at risk of developing calciphylaxis, such as obese, diabetic patients, subcutaneous injections of insulin or heparin in areas that are most likely to experience calciphylaxis lesions (the abdomen and thigh)

should be limited. Frequent injections into adipose tissue, where a vascular bed is already ischemic but not clinically apparent, may promote dystrophic calcification. Patients with established calciphylaxis lesions, in particular those with one small focus of a calciphylaxis lesion, may worsen the lesion if systemic hypotension occurs. Hypotension due to sepsis or surgeries may predispose patients to the development of additional cutaneous ischemic lesions, given the likely inability of diseased vessels to autoregulate well.

For those patients with unresolving skin lesions attributed to calciphylaxis, success of surgical debridement is traditionally poor, perhaps because the skin surrounding the lesions is usually also ischemic. In particular, amputations in patients with calciphylaxis are associated with extremely poor healing rates (146,147). Nevertheless, it is often worth the risk of poor healing to amputate chronically infected tissue if sepsis is present.

Reassess the Use of Warfarin

When warfarin is being used to maintain hemodialysis access graft patency, it may be appropriate to convert a patient to other forms of anticoagulation if they are at risk for calciphylaxis. When warfarin use is chronically needed, as occurs in the setting of prosthetic heart valves, ensuring adequate nutrition and limiting other controllable risk factors is of paramount importance.

Consider Parathyroidectomy

Parathyroidectomy has been shown to heal large vessel calcifications, although such healing understandably takes time (148). Small vessel calcifications, as occur in calciphylaxis, may not heal after parathyroidectomy. A report by DeFrancisco et al. (149) suggests that even 4 years after parathyroidectomy, small vessel calcifications tend not to improve, despite healing of osteitis fibrosa lesions.

A review of the published calciphylaxis cases suggests parathyroidectomy does benefit wound healing (33,64,150) and improves short-term mortality (151,152). The long-term benefits are largely unknown. Most of the benefit appears to be in those individuals with extremely elevated PTH values (e.g., 10 times the upper limit of normal serum PTH values, or higher) (153). As mentioned, much of the improvement following parathyroidectomy in calciphylaxis may be related to a dramatic decrease in serum calcium or phosphorus values. Whether the "hungry bone syndrome" following parathyroidectomy can mobilize dystrophic calcium or improve vascular calcifications has not been well substantiated.

We have observed improvements in transcutaneous oxygen saturations in calciphylaxis patients treated with parathyroidectomy, but only when PTH values were quite elevated (greater than 700 pg/dl) (unpublished observations). The improvements in skin oxygenation were noted within days or a few weeks of surgery. Because an improvement in the appearance of skin lesions has also been noted to occur rapidly (within a few weeks) after parathyroidectomy, a hemodynamic benefit of lowering the PTH values has been suggested (35,152).

Reassess for the Presence of Adynamic Bone

The concern about performing a parathyroidectomy in a patient with a relatively low bone turnover state is appropriate, and patients with PTH values just above an acceptable range for dialysis patients may not benefit from the removal of parathyroid tissue. Rather, such an approach may worsen hyperphosphatemia and/or hypercalcemia by inducing a low turnover state.

Consider Supplemental Oxygen and/or Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) therapy has been reported to cure the cutaneous ulcers of calciphylaxis (154–156). Such benefit would be expected to help with those patients with marginal decreases in blood flow/ischemia of skin, but not other organs. The difficulty with hyperbaric therapy includes availability and cost. We have reported that two calciphylaxis patients who were treated with HBO therapy experienced an increase in pain at the end of the treatment period (23). Whether adjustments in the pressures used in the HBO chamber could lessen the pain was not pursued. Topical hyperbaric therapies are becoming available that obviate the need for total body therapy. To date, no reports of improvement in calciphylaxis skin lesions using topical HBO are available.

Supplemental oxygen, even nasal cannula oxygen, may improve cutaneous oxygen values. This therapy may therefore help improve cutaneous ulcers of calciphylaxis. Our experience is that it also helps improve the cutaneous hyperesthesia that is related to cutaneous nerve ischemia.

Evaluate for Hypercoagulable States

It was noted by Goldsmith (157) that many reported cases of calciphylaxis do not discuss any work-up for a hypercoagulable state, despite the literature that suggests protein C and protein S deficiencies may play a role in lesion development. Also noteworthy is a report that calciphylaxis occurred in a patient with antiphospholipid syndrome (158), an entity that may be treatable with pheresis.

More clinical information is needed to fully implicate derangements in procoagulant or anticoagulant proteins in the pathology of calciphylaxis. To learn more about the potential association with hypercoagulable states, calciphylaxis patients should be evaluated for protein C and protein S antigen deficiencies as well as functional assays of these proteins. Performing a broad hypercoagulable work-up in consultation with a hematologist is appropriate. In addition, very little is known about vitamin K levels in ESRD patients. It may be that relative vitamin K deficiency can cause a procoagulant and even a procalcifying effect in calciphylaxis. In severely malnourished patients or patients who have received broad-spectrum antibiotics prior to calciphy-

laxis presentation, it may be appropriate to administer vitamin K supplementation, given one case report of success (125).

Other Interventions

Despite the Selye et al. model where corticosteroids were considered a "challenger" that caused calcification, one report suggested skin lesions healed in an ESRD patient treated with oral corticosteroids, simultaneous with the improvement of serum calcium and phosphorus balance (159).

Provide Adequate Analgesia

The pain experienced in the skin and subcutaneous tissues by many calciphylaxis patients can be severe and debilitating. Wide areas of a body region may be painful to the lightest pressure or touch. Large doses of analgesics are often needed to provide relief. Given the difficulty in providing relief, some authors have reported a benefit of sympathetic blockade (63). The involvement of a pain consult team is often needed to help provide a rationale therapeutic approach.

Hospice

Calciphylaxis patients often cannot heal the burden of extensive skin necrosis or resolve the infection of open skin wounds. Mortality is generally quite high in calciphylaxis. In our series of 21 calciphylaxis patients (23), the majority of patients died within 10 months of the diagnosis, many after spending considerable time in a hospital. The high mortality rates, refractoriness of infection, and severity of pain in calciphylaxis may make referral to hospice care appropriate.

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