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Calciphylaxis

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Abstract

Purpose of review—Calciphylaxis remains a poorly understood vascular calcification disorder with predilection for patients with end-stage renal disease (ESRD). Recent data from large patient registries and databases have begun to provide information regarding incidence, risk factors, and outcomes in patients with calciphylaxis.

Recent findings—The most recent estimate places the incidence of calciphylaxis at 3.5 new cases/1000 patient-years among the patients with ESRD on chronic hemodialysis. It is possible that misdiagnosis or subclinical disease may attribute to lower than the true incidence. There is a suggestion that the incidence is higher in peritoneal dialysis patients compared with patients with hemodialysis. Recent studies have identified a number of risk factors and point to the effects of vitamin K deficiency mediated impairment in Matrix Gla Protein carboxylation as one of the likely pathogenic mechanisms. The outcomes in calciphylaxis patients remain poor with mortality approaching 30% at 6 months and 50% at 12 months.

Summary—The present review describes recent literature in the field of calciphylaxis. Calciphylaxis registries and specimen biorepositories promise to provide insights into the pathogenesis of calciphylaxis and will pave the way for much needed clinical trials.

Keywords

calcific uremic arteriopathy; matrix gla protein; sodium thiosulfate; vitamin K; warfarin

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriopathy (CUA), is a rare and poorly understood vascular calcification disorder with predilection for patients with end-stage renal disease (ESRD) [1–3]. Case reports of patients with calciphylaxis were first published in the medical literature in 1960s [4,5]. However, the current understanding of calciphylaxis pathogenesis, risk factors, and natural history is limited and there is a striking lack of high-quality data and randomized controlled trials regarding calciphylaxis treatment.

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Conflicts of interest

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Recent findings from large patient registries and databases have begun to address these knowledge gaps as novel methods and collaborative approaches to rare disease research are being applied. There is a tremendous enthusiasm in the field as evidenced by an increase in the calciphylaxis publications in recent years.

The present review summarizes recent literature in the field of calciphylaxis and discusses areas for future research.

INCIDENCE AND PREVALENCE

A recent nation-wide study conducted in the Fresenius Medical Care North America (FMCNA) dialysis units reported calciphylaxis incidence rate of 3.49 per 1000 patient-years among the patients with ESRD on chronic hemodialysis [6]. This study, the largest to date, identified 1030 newly diagnosed calciphylaxis cases in the FMCNA cohort (>250 000 patients with chronic hemodialysis) during a 5-year study period that extended from January 2010 to December 2014. The calciphylaxis incidence rate was calculated by assuming it follows a Poisson distribution and by applying the following equation: incidence rate = number of new calciphylaxis cases/sum of person-follow up time at risk.

A recent report from the German Calciphylaxis Registry recorded calciphylaxis reporting rate of ~30 new cases/year among the dialysis patients from Germany (equal to an annual incidence of ~0.04%) during more than 8-year study period that extended from December 2006 to March 2015 [7]. A Japanese study previously reported a prevalence rate of less than three cases per 10 000 chronic hemodialysis patients per year, a rate much lower than reported studies from the western countries [8].

The above-described reports, with their nationwide data collection and larger sample size compared to previous studies, have overcome limitations to incidence reporting inherent to small sample size and single center studies. However, limitations related to misdiagnosis and underreporting persist as investigators relied on patient's clinicians to report new calciphylaxis cases. Furthermore, following questions remain unanswered:

- (1) What is the calciphylaxis incidence in patients with ESRD treated with peritoneal dialysis and renal transplantation?

In the German Calciphylaxis Registry, 10% of the total calciphylaxis patients had ESRD treated with peritoneal dialysis and 13% of the total patients with calciphylaxis had ESRD treated with renal transplantation [7]. However, specific calciphylaxis incidence rates in patients with peritoneal dialysis and renal transplant were not reported. In a small single center cohort study of 63 patients with ESRD treated with peritoneal dialysis, seven patients developed calciphylaxis during the study period that extended from January 2001 to December 2015 tendering the incidence rate of 9.0 per 1000 patient-years [9]. However, a larger study to investigate calciphylaxis incidence in the patients with ESRD treated with renal replacement modalities other than hemodialysis is needed. If the risk of calciphylaxis is different across different renal replacement therapies, then this will inform future studies and clinical decisions regarding choosing the right renal replacement therapy for an individual patient who is at risk for or has calciphylaxis.

- (2) What is the calciphylaxis incidence in patients with CKD and in those with normal kidney function?

Calciphylaxis, although largely described in patients with ESRD, is not exclusive to the patients with ESRD and has been described in patients with normal kidney function and in those with less advanced chronic kidney disease [10–12]. In the German Calciphylaxis Registry, 10% of the total patients with calciphylaxis had either normal kidney function or had CKD not requiring renal replacement therapy [7[■]]. In a recent single center report from Mayo Clinic, nearly 20% of all patients with calciphylaxis had estimated glomerular filtration rate greater than 60 ml/min [13[■]]. Specific calciphylaxis incidence rates in patients with CKD or in those with normal renal function are not available; however, it is reasonable to conclude that the incidence of calciphylaxis is lower in the patients with non-ESRD compared to the patients with ESRD.

- (3) Is the calciphylaxis incidence increasing?

In the German Calciphylaxis Registry, the calciphylaxis incidence was reportedly stable over a more than 8-year study period [7[■]]. Previous reports from the United States Renal Data System and single center experience have suggested that the incidence of calciphylaxis may be on the rise [14,15]. More longitudinal data (including adjustments for age) are needed to understand the changing trends in calciphylaxis epidemiology and its causes.

CLINICAL PRESENTATION

Severe painful skin lesions (reticulate purpura, plaques, or nodules) typically involving the areas of cutaneous and subcutaneous adiposity and rapid progression to ulcers with black eschar are the hallmark of calciphylaxis presentation. Although skin manifestations dominate the clinical presentation, calciphylaxis is likely a systemic disorder. There are recent case and review descriptions of vascular calcifications involving skeletal muscle, intestines, mesentery, optic nerves, and lungs in calciphylaxis patients [16–19]. What distinguishes patients who have calciphylaxis from the ones that have diffuse cardiovascular calcifications but not calciphylaxis should be a focus of future studies.

RISK FACTORS

ESRD is a definite but not a sole calciphylaxis risk factor. Other reported risk associations include female sex, white race, diabetes mellitus, obesity, autoimmune diseases, thrombophilic disorders, liver disease, hypoalbuminemia, and increased serum aluminium levels, hypercalcemia, hyperphosphatemia, hyperparathyroidism, and adynamic bone disease, increased dialysis vintage, unmet dialysis adequacy parameters, high dialysate calcium bath, vitamin K antagonist (warfarin) therapy, malabsorption disorders, calcium supplements, calcium-based phosphate binders, vitamin D analogues, iron therapy, corticosteroids, subcutaneous injections, teriparatide, and a syndrome referred to as polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome [2,3,10,12,14,20–25]. It is important to emphasize that most of these associations are derived from individual case reports or from small retrospective studies and associations in epidemiological studies do not confirm causality.

Findings from recent large studies provide important insights into the predisposing factors for calciphylaxis [6■,7■,13■,26■]. Table 1 summarizes these findings and highlights important methodological differences that may account for differences in observations from these studies. Future studies are needed to investigate how the risk of calciphylaxis differs across the different modalities of renal replacement therapy, to examine the effects of temporal changes in risk factors (e.g. phosphorous) as they relate to calciphylaxis, and to determine whether risk factors differ for calciphylaxis based on lesion characteristics (e.g. location, ulceration).

PATHOGENESIS

The pathogenesis of calciphylaxis remains unclear. Microvascular calcification and thrombosis are likely the key processes in calciphylaxis pathogenesis [2,26■]. However, the exact sequence and regulators of these processes in calciphylaxis are not known.

Matrix gla protein (MGP), a potent inhibitor of vascular calcification, has attracted attention in the recent calciphylaxis literature. The ability of MGP to inhibit calcification requires the activity of a vitamin K-dependent carboxylase. In a recent study that included 20 patients with hemodialysis with calciphylaxis and 20 controls (hemodialysis patients without calciphylaxis) matched for age, sex, race, and warfarin use, relative cMGP concentration (the fraction of total MGP that was carboxylated) was significantly lower in cases compared to controls [25]. In this study, each 0.1 unit reduction in relative cMGP concentration was associated with a more than two times increase in calciphylaxis risk. Another recent small study also observed a trend towards increased skin tissue MGP expression in calciphylaxis [27]. In a previous study, remarkable upregulation of osteogenesis-associated markers and extensive matrix remodeling of the subcutaneous tissue was noted in calciphylaxis dermal tissue [28]. The cross-sectional nature and small sample size of these studies limit causality inference and warrants future confirmation. Future studies are also needed to determine whether mechanisms of calciphylaxis differ based on lesion characteristics and for different possible risk factors (e.g. vitamin K antagonist associated calciphylaxis vs. calciphylaxis not associated with vitamin K antagonist exposure).

DIAGNOSIS

A high index of suspicion is required for calciphylaxis diagnosis. Skin biopsy is the current gold standard for diagnosis; however, future studies are needed to establish histological diagnostic features and careful risk–benefit assessment is needed [2,29]. There are also recent preliminary reports of noninvasive diagnostic modalities (nuclear bone scan, mammography, X-ray, computed tomography, ultrasound, and Raman spectroscopy) that need future investigation [30–33].

In the current clinical practice, clinicopathological correlation is recommended to rule out clinical mimics such as warfarin necrosis, purpura fulminans, atheroembolic disease, antiphospholipid antibody syndrome, peripheral artery disease, vasculitis, and necrotizing infections.

TREATMENT

A multimodal and multidisciplinary approach that comprises of various specialists (nephrologist, dermatologist, pain specialist, palliative care specialist, and wound care specialist) and one that specifically addresses pain and wound management, risk factor elimination (e.g. warfarin discontinuation), and nutrition is previously described [2,3]. Pain management remains challenging in this population as pain is frequently resistant to potent analgesics including opiates [34].

Previous and recent data regarding the efficacy of interventions including intravenous sodium thiosulfate, intralesional sodium thiosulfate, bisphosphonates, vitamin K, surgical debridement, dermal regenerative template, hyperbaric oxygen, surgical parathyroidectomy, novel anticoagulants, renal transplantation, becaplermin (recombinant platelet-derived growth factor), and prostaglandins are derived from retrospective cohort studies, case series, or case reports [2,7,13,35–48]. These interventions need further investigation and at present it is best to adopt a case by case approach that takes into account risk–benefits and limitations of the currently available treatments in the management of calciphylaxis.

A remarkable lack of clinical trials in the field of calciphylaxis reflects the challenges involved in investigating a rare disease and limited understanding of calciphylaxis pathogenesis. However, considering the morbidity and mortality associated with calciphylaxis, there is an urgent need to test the current and new therapies in clinical trials as fittingly emphasized in a recent report by Brandenburg *et al.* [49]. Early clinical trials are underway to investigate the novel treatments such as phytonadione/vitamin K1 supplementation ([ClinicalTrials.gov](#) ID: NCT02278692) and phytate infusion in calciphylaxis ([ClinicalTrials.gov](#) ID: NCT02790073) [50–52]. Furthermore, prospective registries such as the Partners Calciphylaxis Biobank ([ClinicalTrials.gov](#) ID: NCT03032835), EuCalNet ([ClinicalTrials.gov](#) ID: NCT02635373), and CalciWest ([ClinicalTrials.gov](#) ID: NCT02854046), and Australian Calciphylaxis Registry are now available to systematically follow outcomes from different treatments and offer a platform for future pragmatic trials [53–56].

PROGNOSIS

The outcomes in calciphylaxis patients remain poor with mortality rate at approximately 30% at 6 months and 50% at 12 months [6,13]. Septicemia from the infected wounds is the leading cause of death. The morbidity in calciphylaxis is related to severe pain, advanced wounds, and recurrent hospitalizations. Determinants of prognosis in calciphylaxis patients needs future investigation.

CONCLUSION

The present review describes recent literature in the field of calciphylaxis. The previous sample size limitation of calciphylaxis research is now beginning to get addressed by large calciphylaxis registries and national level databases. As a result, better quality data are now available regarding calciphylaxis incidence, risk factors, and outcomes. The registries and

biorepositories promise to provide insights into the pathogenesis of calciphylaxis and will pave the way for much needed clinical trials.

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KEY POINTS

- Calciphylaxis is a rare but highly fatal vascular calcification disorder with predilection for the patients with ESRD.
- Vitamin K deficiency via its effects on MGP carboxylation may increase the risk of calciphylaxis.
- Future investigations from calciphylaxis registries and biorepositories are needed to understand the exact pathogenesis of calciphylaxis and to guide the development of novel treatment approaches.

Table 1

A summary of methods, results, and limitations of recent studies investigating calciphylaxis risk factors

Study	Design	Population	Main findings	Limitations
Nigwekar <i>et al.</i> [6■]	Case-control study Baseline factors recorded at hemodialysis initiation were analyzed as potential calciphylaxis risk factors.	Cases: Chronic hemodialysis patients with newly diagnosed calciphylaxis ($n = 1030$) Controls: Chronic hemodialysis patients without calciphylaxis matched to cases for age, sex, and race ($n = 2060$) Cases and controls were identified from the dialysis units affiliated with the FMCNA, a large national-level dialysis provider.	Mean age for cases and controls were 54 and 55 years, respectively; 67% of participants were women and 49% were white. Median duration between hemodialysis initiation and subsequent calciphylaxis development was 925 days (interquartile range, 273–2185 days). In multivariable analyses, diabetes mellitus; higher body mass index; higher levels of serum calcium, phosphorous, and parathyroid hormone; and nutritional vitamin D, cinacalcet, and warfarin treatments were associated with increased risk of subsequent calciphylaxis development. Compared with patients with diabetes receiving no insulin injections, those receiving insulin injections had a dose-response increase in the risk of calciphylaxis involving lower abdomen and/or upper thigh areas.	-Residual confounding -Survivorship bias -Lack of repeated measures analyses
Brandenburg <i>et al.</i> [7■]	Cohort study Data were recorded at or closely prior to calciphylaxis diagnosis.	Calciphylaxis patients ($n = 253$) identified from a prospective internet-based registry allowing online notification for all German calciphylaxis cases.	Median age of calciphylaxis patients was 70 years and 60% were females. 86% were dialysis patients 52% received vitamin K antagonists prior to calciphylaxis development. Mineral bone parameters including parathyroid hormone levels were remarkably close to normal range.	-Lack of control group -Reporting bias -Lack of repeated measures analyses
McCarthy and El-Azhary <i>et al.</i> [13■,26■]	Cohort study Data were recorded at or within 12 months prior to calciphylaxis diagnosis.	Calciphylaxis patients ($n = 101$) identified retrospectively from an institutional database of a large academic center.	Mean age of calciphylaxis patients was 60 years, 80% were women. 68% were obese. 19% had stage 0 to 2 chronic kidney disease, 1 9% had stage 3 or 4 chronic kidney disease; 62% had stage 5 or 5D (dialysis) chronic kidney disease. 60% had severe thrombophilia.	-Lack of control group -Single center experience -Lack of availability of longitudinal data prior to presentation