

Calciophylaxis in peritoneal dialysis patients: a single center cohort study

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Background: Calciophylaxis is a rare but devastating condition in end-stage renal disease (ESRD) patients. Most research in the field of calciophylaxis is focused on hemodialysis (HD) patients; however, data on calciophylaxis incidence, risk factors, and mortality in peritoneal dialysis (PD) patients are limited.

Methods: In this cohort study, we examined data from adult patients who initiated PD for ESRD management at our institute's PD unit from January 2001 to December 2015. Associations with the development of calciophylaxis were examined for clinical, laboratory, and medication exposures. Incidence of calciophylaxis and mortality in PD patients who developed calciophylaxis were analyzed. Treatments administered to treat calciophylaxis in PD patients were summarized.

Results: In this cohort of 63 patients, 7 patients developed calciophylaxis (incidence rate: 9.0 per 1,000 patient-years). Median age of PD patients who developed calciophylaxis was 50 years, 57% were white, 71% females, and 71% were previously on HD. Female sex, obesity, HD as a prior dialysis modality, recurrent hypotension, elevated time-averaged serum phosphorous levels, reduced time-averaged serum albumin levels, and warfarin therapy were associated with increased calciophylaxis risk in univariate logistic regression analyses. Intravenous sodium thiosulfate was administered in 57% of PD patients who developed calciophylaxis. One-year mortality in PD patients who developed calciophylaxis was 71% despite multimodal treatment including sodium thiosulfate, hyperbaric oxygen, cinacalcet, and wound debridement.

Conclusion: Calciophylaxis is a rare but frequently fatal condition in PD patients. Our study provides critical early insights into calciophylaxis incidence, risk factors, and prognosis in PD patients. Sample size and characteristics of patients included in our study limit generalizability to overall PD population and warrant examination in larger independent studies.

Keywords: calcific uremic arteriopathy, dialysis, hypotension, warfarin

Introduction

Calciophylaxis also known as calcific uremic arteriopathy is a highly fatal condition characterized by dermal arteriolar calcification and thrombosis.¹ Calciophylaxis is predominantly seen in patients with end-stage renal disease (ESRD) and it remains an enigmatic disorder with obscure pathogenesis.²

Recent reports describing epidemiology, clinical characteristics, and treatments for calciophylaxis have focused largely on hemodialysis (HD) patients. These data suggest that the incidence of calciophylaxis in HD patients is approximately 3.5 cases per 1,000 patient-years and it may be on the rise.^{3,4} Diabetes mellitus, obesity, abnormalities in mineral bone parameters, and warfarin therapy have been described as calciophylaxis risk factors for HD patients.^{3,5-7} Cinacalcet has been reported to reduce the risk

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of calciphylaxis in HD patients and intravenous sodium thiosulfate has been described to be associated with clinical improvement of calciphylaxis in HD patients.^{8–11} However, corresponding data regarding epidemiology, clinical characteristics, and treatments for calciphylaxis in peritoneal dialysis (PD) patients are limited despite an earlier suggestion that PD patients may be at a higher risk for calciphylaxis compared to HD patients.^{12,13} Understanding the risk factors and outcomes of calciphylaxis in PD patients is critical to the development of future interventions to prevent and treat calciphylaxis, especially as the reasons for an apparent increase in calciphylaxis risk in PD patients are unclear. Therefore, we undertook the present cohort study to describe calciphylaxis incidence, risk factors, therapies, and mortality in PD patients at our center.

Methods

Partners Human Research Committee approved this study, the need for patient consent was waived for this minimal risk retrospective study. We retrospectively evaluated medical records of all adult (age >18 years) patients who initiated PD for ESRD management at our institute's PD unit during the study period from January 1, 2001 to December 31, 2015. Patients who developed calciphylaxis were identified by applying a previously published algorithm that incorporates natural language processing and by manual chart review.⁴ Diagnosis of calciphylaxis was clinically suspected and had histopathological confirmation in all patients. Data regarding demographics, vital signs, comorbidities, dialysis and ESRD-related characteristics, medications and mineral bone parameters, and nutritional parameters were abstracted from the medical record. Laboratory data were time-averaged for each patient as follows: for patients who developed calciphylaxis, laboratory data were time-averaged from the PD initiation to the diagnosis of calciphylaxis and for patients who did not develop calciphylaxis, laboratory data were time-averaged from the PD initiation to the last available laboratory data. Serum calcium levels were corrected for albumin.¹⁴ Data for warfarin and medications administered to manage mineral bone abnormalities were abstracted from the time of PD initiation. In addition for PD patients who developed calciphylaxis, ESRD vintage (time between onset of ESRD and development of calciphylaxis) and PD vintage (time between start of PD and development of calciphylaxis) were computed and data regarding calciphylaxis lesions, treatments administered to treat calciphylaxis, and one-year mortality were summarized. A single investigator conducted data abstractions and another investigator independently confirmed data accuracy.

Median with interquartile range (IQR) and frequency percentages were reported for continuous and categorical

variables, respectively. We calculated calciphylaxis incidence rate per 1,000 patient-years by assuming it follows a Poisson distribution and applying the following equation: calciphylaxis incidence = (number of new calciphylaxis cases) ÷ (sum of person-follow-up time at risk). Categorical variables were compared between patients with and without calciphylaxis using a Fisher's exact test and continuous variables were compared using a Mann–Whitney *U* test. Univariate logistic regression models were applied to compute odds ratio (OR) and 95% confidence intervals (CI) to test the association between risk factors and calciphylaxis development.

Analyses were performed using SAS, version 9.4. Statistical significance was set at $P < 0.05$.

Results

Incidence and characteristics of PD patients who developed calciphylaxis

Our cohort comprised of 63 adult PD patients. During the study period, we identified seven patients who developed calciphylaxis tendering calciphylaxis incidence of 9.0 per 1,000 patient-years in PD patients.

Characteristics of individual PD patients who developed calciphylaxis are tabulated in Table 1. Median age was 50 years (IQR: 34–59), 57% were white, 71% females, and 43% had diabetes mellitus. Median body mass index was 31.3 kg/m² (IQR: 23.7–32.8), median ESRD vintage was 5.2 years (IQR: 4.1–14.3), and median PD vintage was 4.1 years (IQR: 3.2–7.0). Most patients (71%) were previously on HD and were transitioned to PD for access failure or for inability to tolerate HD. Recurrent episodes of severe hypotension (systolic blood pressure <80 mmHg) preceding calciphylaxis were recorded in 43% and 67% of patients who had recurrent severe hypotension were previously on HD. None of the PD patients who developed calciphylaxis were on automated PD and all of them were on 2.5 mEq/L calcium dialysate. Although no patient had residual urine output at the time of calciphylaxis diagnosis, 86% had weekly Kt/Vurea at the recommended goal of ≥ 1.70 .¹⁵ Median levels of time-averaged mineral metabolism parameters were as follows – albumin-corrected serum calcium: 9.8 mg/dL (IQR: 7.9–10.8), phosphorous: 6.1 mg/dL (IQR: 4.8–6.9), and intact parathyroid hormone: 270 pg/mL (IQR: 213–657). Median levels of time-averaged nutritional parameters were as follows – serum albumin: 3.1 g/dL (IQR: 2.6–3.2) and normalized protein catabolic rate: 0.78 g/kg/day (IQR: 0.67–0.83). At the time of PD initiation, 71% of PD patients who subsequently developed calciphylaxis were on warfarin, 86% on active vitamin D, 29% on calcium-based phosphate binder,

Table 1 Characteristics of PD patients who developed calciophylaxis

Characteristic	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age, years	50	41	34	59	65	57	30
Sex	Female	Female	Male	Female	Female	Male	Female
Race	White	Black	White	Black	White	Black	White
Etiology of ESRD	Oligonephronia	Lupus	Lupus	Unknown	Diabetes	Diabetes	Primary FSGS
Diabetes mellitus	Yes	No	No	No	Yes	Yes	No
Body mass index, kg/m ²	27.0	31.3	20.0	32.0	32.9	23.7	32.8
Recurrent severe hypotension (SBP<80 mmHg)	Yes	No	No	Yes	Yes	No	No
ESRD vintage, years	32.0	14.3	4.1	5.2	4.8	5.3	3.2
Prior HD therapy	Yes	Yes	Yes	Yes	No	Yes	No
PD vintage, years	8.0	7.0	3.4	4.1	4.8	2.1	3.2
Weekly Kt/Vurea	1.98	2.12	1.61	1.99	2.06	2.02	2.71
Serum calcium, mg/dL [†]	9.8	9.3	7.0	10.8	10.3	10.9	7.9
Serum phosphorous, mg/dL	6.3	5.7	6.9	4.8	7.2	6.1	3.6
Serum intact PTH, pg/mL	213	657	89	234	270	678	543
Serum albumin, g/dL	2.2	2.8	3.2	4.1	3.1	2.6	3.2
Normalized protein catabolic rate, g/kg/day	0.81	0.67	0.83	0.67	0.87	0.78	0.75
Warfarin therapy	Yes	Yes	No	Yes	No	Yes	Yes
Active vitamin D agent therapy	Yes	Yes	Yes	Yes	No	Yes	Yes
Calcium-based phosphate binder therapy	No	No	Yes	No	No	No	Yes
Cinacalcet therapy	No	Yes	No	No	No	Yes	No
Location(s) of calciophylaxis lesion(s)	Bilateral toes	Calf, foot	Shin	Thigh	Thigh, abdomen	Penis	Bilateral thighs, forearms
Vital status 1 year after calciophylaxis diagnosis	Dead	Alive	Dead	Dead	Dead	Dead	Alive

Note: [†]Serum calcium levels are corrected for serum albumin levels.

Abbreviations: ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; PD, peritoneal dialysis; PTH, parathyroid hormone; SBP, systolic blood pressure.

and 29% were on cinacalcet. The indications for warfarin therapy for PD patients who developed calciophylaxis included atrial fibrillation (n=3, 60%) and venous thromboembolic disease from antiphospholipid antibody syndrome (n=2, 40%).

The number of calciophylaxis skin lesion(s) for each patient ranged from 1 to 6. Lesions exhibited both proximal and distal distributions but none involved the site of PD catheter insertion. At the time of calciophylaxis diagnosis, all skin lesions were ulcerated and had a black eschar characteristic of calciophylaxis as illustrated in Figure 1.

Risk factors for calciophylaxis in PD patients

As summarized in Table 2, PD patients who developed calciophylaxis were more likely to be female (71% vs 30%, $P=0.032$) and had higher frequencies of obesity (57% vs 20%, $P=0.031$), prior history of being on HD (71% vs 30%, $P=0.032$), prior episodes of recurrent hypotension (43% vs 7%, $P=0.004$), and warfarin therapy exposure (71% vs 16%, $P=0.001$). Review of echocardiographic data from calciophylaxis PD patients with recurrent episodes of hypotension showed that all of these patients had symmetric left ventricular hypertrophy and reduced left ventricular ejection fraction (range: 20–32%). Calciophylaxis patients had



Figure 1 A representative image showing an ulcerated calciophylaxis lesion with black eschar in a peritoneal dialysis patient.

higher time-averaged serum phosphorous levels and lower time-averaged serum albumin levels. Other characteristics were comparable between PD patients with and without calciophylaxis development.

Results of the univariate logistic regression analyses which focused on covariates with statistically significant differences between PD patients with and without calciophylaxis development are listed in Table 3. Among all the covariates with statistically significant association with calciophylaxis

Table 2 Comparison of characteristics between PD patients who developed calciphylaxis and PD patients who did not develop calciphylaxis

Characteristic	Calciphylaxis (n=7)	No calciphylaxis (n=56)	P-value
Age, years	50 (IQR: 34–59)	54 (IQR: 39–70)	0.941
Female sex, %	71	30	0.032
White race, %	57	63	0.621
Diabetes mellitus, %	43	41	0.881
Obesity, %	57	20	0.031
Recurrent severe hypotension, %	43	7	0.004
Prior HD therapy, %	71	30	0.032
Weekly Kt/Vurea	2.02 (IQR: 1.98–2.12)	2.10 (IQR: 1.89–2.35)	0.781
Serum calcium, mg/dL [†]	9.8 (IQR: 7.9–10.8)	9.0 (IQR: 8.5–10.1)	0.563
Serum phosphorous, mg/dL	6.1 (IQR: 4.8–6.9)	3.2 (IQR: 2.2–3.9)	0.023
Serum intact PTH, pg/mL	270 (IQR: 213–657)	291 (IQR: 182–452)	0.601
Serum albumin, g/dL	3.1 (IQR: 2.6–3.2)	3.7 (IQR: 3.6–4.6)	0.049
Normalized protein catabolic rate, g/kg/day	0.78 (IQR: 0.67–0.83)	1.01 (IQR: 0.80–1.06)	0.092
Warfarin therapy, %	71	16	0.001
Active vitamin D agent therapy, %	86	49	0.821
Calcium-based phosphate binder therapy, %	29	33	0.512
Cinacalcet therapy, %	29	30	0.672

Note: [†]Serum calcium levels are corrected for serum albumin levels.

Abbreviations: HD, hemodialysis; IQR, interquartile range; PD, peritoneal dialysis; PTH, parathyroid hormone.

Table 3 Results from univariate logistic regression analyses showing risk associations with statistical significance for calciphylaxis development in PD patients

Covariate	OR	95% CI
Female sex	5.74	1.01–32.54
Obesity	5.45	1.06–27.99
Recurrent severe hypotension	9.75	1.60–59.56
Prior HD therapy	5.74	1.01–32.54
Serum phosphorous (per 1 mg/dL increase)	2.13	1.01–4.56
Serum albumin (per 1 g/dL reduction)	2.21	1.02–3.65
Warfarin therapy	13.06	2.18–78.05

Abbreviations: CI, confidence intervals; HD, hemodialysis; PD, peritoneal dialysis; OR, odds ratio.

risk, warfarin therapy was associated with the highest risk for calciphylaxis (OR: 13.06, 95% CI: 2.18–78.05).

Calciphylaxis treatments and mortality in PD patients

All PD patients who developed calciphylaxis underwent dressing changes and chemical debridement, and received opiate analgesics and nutrition consultations as shown in Figure 2. Surgical debridement was conducted in 43%, 57% received hyperbaric oxygen, and 43% were transitioned to HD. Intravenous sodium thiosulfate was administered in 57% patients including in patients who did not transition from PD to HD; none received intraperitoneal or intralesional sodium thiosulfate. Intravenous sodium thiosulfate was administered in our PD unit either through peripheral or central venous access. All patients who received intravenous sodium

thiosulfate received it as 25 g (mixed in 100 mL of normal saline to be infused over 2 hours) 3 times a week. Median duration of intravenous sodium thiosulfate treatment was 3.0 months (IQR: 2.8–5.1). Among the four patients who were treated with intravenous sodium thiosulfate, one reported nausea and vomiting. There were no other side effects recorded from intravenous sodium thiosulfate use. Serum bicarbonate levels in four patients who received intravenous sodium thiosulfate were reduced by an average of 3.5 mEq/L during intravenous sodium thiosulfate therapy.

One-year mortality in PD patients who developed calciphylaxis was 71%; all deaths were due to sepsis. One-year mortality rate was 67% in patients who underwent surgical debridement, 50% in patients who received hyperbaric oxygen, 75% in patients treated with intravenous sodium thiosulfate, and 100% in patients who transitioned from PD to HD.

Discussion

Despite first descriptions of calciphylaxis over 5 decades ago, little is known regarding its epidemiology and risk factors in PD patients.^{1,13,16,17} Our study was designed to address this knowledge gap. In our single center cohort of 63 PD patients, 7 patients developed calciphylaxis during the 15-year study follow-up period. We noted a number of potential risk factors for calciphylaxis in PD patients. One-year mortality in PD patients who developed calciphylaxis was 71% despite multimodal treatment.

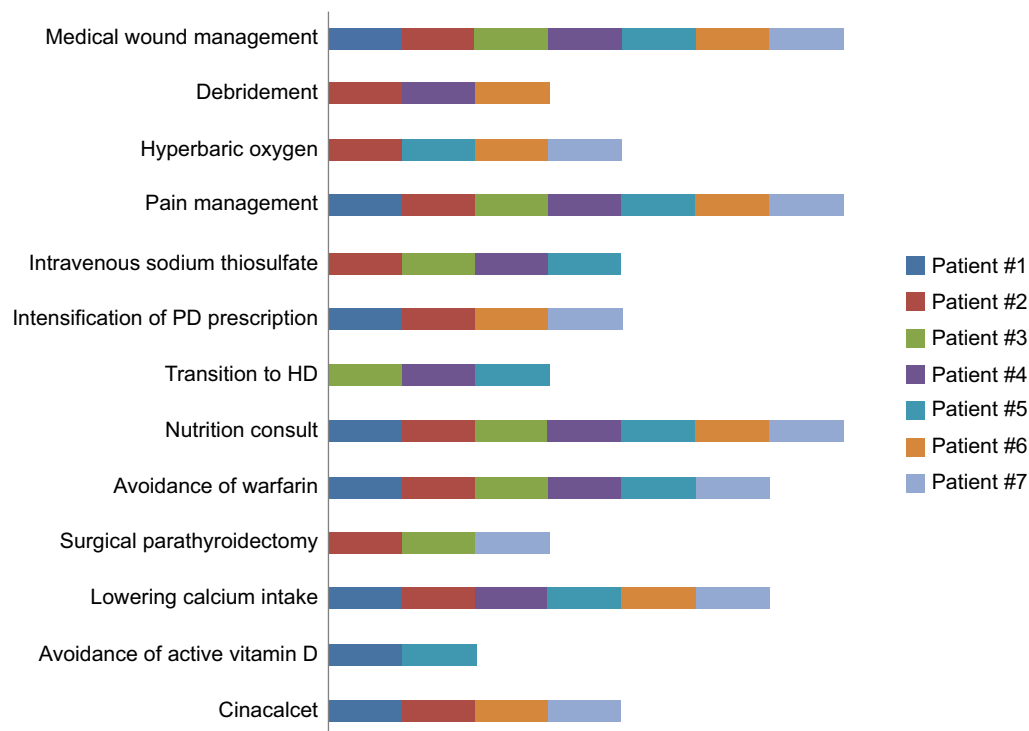


Figure 2 Components of multimodal treatment administered to PD patients who developed calciophylaxis. **Abbreviations:** PD, peritoneal dialysis; HD, hemodialysis.

Calciophylaxis incidence rate of 9.0 per 1,000 patient-years in our PD cohort is higher than the recently reported calciophylaxis incidence in HD patients of 3.5 cases per 1,000 patient-years.^{4,9,18} Considering the sample size limitation of our study and single center experience, definitive conclusions regarding comparative effectiveness of PD vs HD for calciophylaxis risk cannot be made; however, our study adds to the debate in the literature regarding whether PD as a dialysis modality confers a higher calciophylaxis risk than HD.^{12,13,19} It is important to note that although PD was the dialysis modality for our study patients when calciophylaxis was diagnosed, many patients were previously on HD and required transition to PD for access failure or recurrent hypotension. In that regard, these were likely “the sickest of the sick” ESRD patients and our findings may not be generalizable to the overall PD population. Change in dialysis modality per se has been described to be associated with worse outcomes such as mortality.²⁰ Furthermore, prevalence of well-described calciophylaxis risk factors such as warfarin therapy and obesity was higher in PD patients who developed calciophylaxis compared to previously published prevalence of these risk factors in HD patients who developed calciophylaxis.^{3,5–7,18} Thus, it is possible that it is these risk factors and not dialysis modality that dictates calciophylaxis risk. Previous studies have shown that PD is associated with more abnormalities in phosphorous and albumin than HD, especially once residual

renal function has deteriorated.^{21,22} Thus, it is possible that our data suggest that those PD patients who have difficulty controlling phosphorus or maintaining their albumin may be at increased risk of calciophylaxis.

The potential risk associations observed in our study may be instructive to understand calciophylaxis pathobiology. Warfarin (vitamin K antagonist) as a potential risk factor suggests a critical role of vitamin K-dependent proteins such as MGP in the inhibition of vascular calcification.²³ Recurrent episodes of hypotension preceding calciophylaxis development may point toward reduced perfusion serving as a trigger for ischemia in dermal beds with calcified arterioles. Low normalized protein catabolic rate and serum albumin in PD patients who developed calciophylaxis may implicate that the malnutrition–inflammation complex is at play.^{24,25}

It is likely that in our study, a statistically significant difference between PD patients with and without calciophylaxis was not noted due to limited sample size and one-time assessment (at PD initiation) of certain covariates such as medications. This is particularly important as the pathogenesis of calciophylaxis is likely multifactorial, as supported by larger studies^{3,6} in the HD population that noted multiple calciophylaxis risk factors, including diabetes mellitus and advanced age. Small sample size also limited us from conducting multivariable adjusted analyses to examine whether associations observed in univariate analyses

remain consistent when adjusted for other covariates. Larger studies are needed to ascertain calciphylaxis risk in PD vs HD patients and to confirm risk associations observed in our study. These future studies should be multicenter to improve generalizability, should include assessments of novel dynamics such as recurrent hypotension, echocardiographic parameters, and PD technique (eg, automated PD vs continuous ambulatory PD), and should investigate longitudinal effects of residual kidney function and medications. Given the mortality associated with calciphylaxis, identifying patient and modality characteristics that may confer increased risk is important when helping patients choose a dialysis modality.

In our study, PD patients who developed calciphylaxis received multimodal treatment. Although successful calciphylaxis improvement has been reported with such multimodal treatment, our patients had a high mortality rate.^{26–28} This could be reflective of high mortality due to ulcerated calciphylaxis lesions and/or the overall poor prognosis in patients with recurrent hypotension. Alternative methods of sodium thiosulfate administration were not applied in our study patients, considering the potential risk of further ulceration (with intralesional) and concern for chemical peritonitis (with intraperitoneal).^{29–32}

In conclusion, calciphylaxis is a rare but fatal complication in PD patients. Our study provides insights into calciphylaxis epidemiology and risk factors in PD patients and motivates future investigation.

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Disclosure

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