

Risk factors and mortality associated with calciphylaxis in end-stage renal disease

A. RAUF MAZHAR, RICHARD J. JOHNSON, DANIEL GILLEN, JOHN C. STIVELMAN, MICHAEL J. RYAN, CONNIE L. DAVIS, and CATHERINE O. STEHMAN-BREEN

University of Washington, Division of Nephrology, Seattle, Washington; Baylor College of Medicine, Division of Nephrology, Houston, Texas; Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Northwest Kidney Centers, and Division of Nephrology, Puget Sound Health Care System, Seattle, Washington, USA

Risk factors and mortality associated with calciphylaxis in end-stage renal disease.

Background. We conducted a case control study to determine risk factors and mortality associated with calciphylaxis in end-stage renal disease.

Methods. Cases of calciphylaxis diagnosed between December 1989 and January 2000 were identified. Three controls were identified for each hemodialysis patient, with calciphylaxis matched to the date of initiation of hemodialysis. Laboratory data and medication doses were recorded during the 12 months prior to the date of diagnosis and at the time of diagnosis of calciphylaxis. Conditional logistic regression was used to identify risk factors for calciphylaxis. Cox proportional hazards models were used to estimate the risk of death associated with calciphylaxis.

Results. Nineteen cases and 54 controls were identified. Eighteen patients were hemodialysis patients, and one had a functioning renal allograft. Diagnosis was confirmed by skin biopsy in 16 cases. Women were at a sixfold higher risk of developing calciphylaxis (OR = 6.04, 95% CI 1.62 to 22.6, $P = 0.007$). There was a 21% lower risk of calciphylaxis associated with each 0.1 g/dL increase in the mean serum albumin during the year prior to diagnosis and at the time of diagnosis of calciphylaxis (OR = 0.79, 95% CI, 0.64 to 0.99, $P = 0.037$, and OR = 0.80, 95% CI, 0.67 to 0.96, $P = 0.019$, respectively). There was a 3.51-fold increase in the risk of calciphylaxis associated with each mg/dL increase in the mean serum phosphate during the year prior to diagnosis (95% CI, 0.99 to 12.5, $P = 0.052$). At the time of diagnosis of calciphylaxis, for each 10 IU/L increment in alkaline phosphatase, the risk of calciphylaxis increased by 19% (OR = 1.19, 95% CI, 1.00 to 1.40, $P = 0.045$). Body mass index, diabetes, blood pressure, aluminum, and higher dosage of erythropoietin and iron dextran were not independent predictors of calciphylaxis. Calciphylaxis independently increased the risk of death by eightfold (OR = 8.58, 95% CI, 3.26 to 22.6, $P < 0.001$).

Key words: hyperphosphatemia, alkaline phosphatase and calciphylaxis, serum albumin and calciphylaxis, death and calciphylaxis, skin lesions and mortality.

Received for publication October 26, 2000
and in revised form February 7, 2001
Accepted for publication February 9, 2001

© 2001 by the International Society of Nephrology

Conclusions. Female gender, hyperphosphatemia, high alkaline phosphatase, and low serum albumin are risk factors for calciphylaxis. Calciphylaxis is associated with a very high mortality.

Calciphylaxis is a condition that has been recognized and reported in the end-stage renal disease (ESRD) population with increasing frequency in the last decade [1–5]. It is characterized by painful and pruritic skin lesions, subcutaneous nodules, skin necrosis, ulceration, and eschar formation. Medial calcification and intimal proliferation of small arteries are observed in skin biopsies of patients with calciphylaxis [3, 4, 6]. In the early 1960s, Selye, Gabbiani, and Strebel described an animal model of calciphylaxis in which sensitization by a systemic calcifying factor such as vitamin D compounds or parathyroid hormone, followed by topical treatment with certain challengers, caused an acute local calcinosis followed by inflammation and sclerosis [7]. Selye, Gabbiani, and Strebel's studies suggested that the uremia in nephrectomized rats with intact parathyroid glands may sensitize and thus promote the development of calciphylaxis. However, the absence of vascular calcification in Selye, Gabbiani, and Strebel's model of experimental calciphylaxis has led some authors to suggest alternative terms such as "calcific uremic arteriolopathy" for human lesions. Calciphylaxis is associated with high morbidity and mortality resulting primarily from local and systemic infections. The pathogenesis and risk factors for calciphylaxis remain poorly understood. Reports have suggested an association between calciphylaxis and elevated parathyroid hormone levels, elevated serum phosphate levels, and elevated calcium-phosphate products in many but not all patients with this condition [3, 6]. Parathyroidectomy is the only therapeutic modality known to improve outcome in some patients with calciphylaxis [1, 6]. Although several factors have been postulated to predispose patients to calciphylaxis, the majority of studies

have been uncontrolled, and there have been no studies estimating the relative risk of mortality associated with calciphylaxis. We conducted a case control study to identify risk factors and to estimate the risk of death associated with calciphylaxis.

METHODS

Study population

Cases. Nineteen patients diagnosed with calciphylaxis between December 1989 and January 2000 at the University of Washington Medical Center, Harborview Medical Center, and Swedish Hospital in Seattle (WA, USA) were identified. Sixteen patients underwent skin biopsies and had histologic evidence of calciphylaxis. All but one patient had been on chronic hemodialysis prior to the diagnosis of calciphylaxis. The remaining patient had a functioning cadaveric renal allograft. All patients were treated with conservative management, including pain control, wound debridement and dressings, antibiotics, discontinuation of calcium salts and vitamin D preparations, phosphate restriction, and a lower calcium concentration in the dialysate. Six patients underwent parathyroidectomy.

Controls. The controls were identified from the patients receiving hemodialysis at the Northwest Kidney Center (NWKC) in Seattle (WA, USA). Three controls ($N = 54$) were identified for each case ($N = 18$) and matched for the date of initiation of hemodialysis (± 2 months). The controls were required to be alive on the dates corresponding to the dates of diagnosis of calciphylaxis for the corresponding case. A control was not identified for the transplant patient.

Data collection

A retrospective review of the hospital and dialysis records of all cases and controls was performed. The following demographic data were abstracted: age, gender, and race (African American, Caucasian, other). Medical data abstracted included primary cause of ESRD (diabetes mellitus, hypertension, glomerulonephritis, other), date of first ESRD treatment, treatment modality (hemodialysis, peritoneal dialysis, renal transplant), and history of diabetes. The height and weight at the time of diagnosis of calciphylaxis (and at the corresponding time for controls) were recorded.

Among patients with parathyromatosis, a history of hypercoagulable states (deficiencies of protein C, protein S, and antithrombin III, lupus inhibitor, antiphospholipid syndromes, and factor II and factor V mutations) was ascertained from the medical records when available. The clinical features (pain, pruritus, rash, ulceration, eschar formation, infected lesions) and histologic features (calcification of small arteries, intimal hyperplasia, skin necrosis, fat necrosis) of calciphylaxis were recorded for

all cases. The lesions were categorized as proximal (extremities proximal to knees and elbows, trunk, breast, and penile) and distal (extremities distal to knees and elbows). The management of pain and lesions (conservative vs. parathyroidectomy) was also recorded.

The following data were abstracted at the time of diagnosis of calciphylaxis and as mean values over the 12 months preceding the date of diagnosis: predialysis systolic and diastolic blood pressures, serum calcium, serum phosphate, calcium-phosphate product, intact parathyroid hormone (iPTH) level, serum albumin, serum alkaline phosphatase, and serum aluminum levels. The medications recorded at the time of diagnosis of calciphylaxis included intravenous iron, oral and intravenous vitamin D preparations, erythropoietin, and warfarin. The cumulative dosage of intravenous iron, intravenous vitamin D preparations, and erythropoietin for 12 months preceding the date of diagnosis of calciphylaxis was also recorded. The data listed here were abstracted for each control using the date of diagnosis of calciphylaxis for the corresponding case.

Outcome measures

The diagnosis of calciphylaxis was based on the presence of painful and pruritic skin lesions and subcutaneous nodules complicated by ulceration and eschar formation in advanced stages of the condition. The diagnosis was confirmed by the presence of medial calcification and intimal hyperplasia of small arteries (subcutaneous and digital) and cutaneous and fat necrosis on skin biopsy in 16 patients (84%). The occurrence and cause of death were determined from the Health Care Financing Administration ESRD Death Notification Form (HCFA-2746).

Statistical analysis

Body mass index (BMI) at the time of diagnosis of calciphylaxis in cases and at the corresponding dates for controls was calculated from height and weight (kg/m^2). Calcium was corrected for serum albumin (serum calcium ± 0.6 mg/dL for each 1 g/L of serum albumin above or below 4 g/dL). The calcium-phosphate product was calculated using serum calcium levels corrected for serum albumin. The duration of chronic renal replacement therapy was calculated as the difference between the date of the first treatment for ESRD and the date of diagnosis of calciphylaxis for each case. The duration of ESRD treatment for each control was calculated as the difference between the date of first treatment for ESRD and the date of diagnosis of calciphylaxis for the corresponding case.

Laboratory and medication data were available at the time of diagnosis and for the 12 months prior to the diagnosis of calciphylaxis. To summarize data generated over the 12 months prior to diagnosis, laboratory values were

averaged, while medication doses were summed. For descriptive purposes, patients were grouped by disease status, and patient characteristics were grouped as being measured prior to and at the time of diagnosis of calciphylaxis. The continuous data are summarized as mean and standard deviation. A comparison of baseline characteristics across disease groups was performed using chi-square tests for discrete variables, two-sample *t* tests for normally distributed continuous variables, and non-parametric permutation tests for highly skewed continuous variables.

Multivariate analysis was performed on the 18 hemodialysis patients and 54 controls. The predictors of developing calciphylaxis were determined using conditional logistic regression due to the matched case-control study design. The univariate regression model estimates, including odds ratios, 95% confidence intervals, and *P* values to test association, are presented for all available predictors. The *P* values presented for univariate results were not adjusted for multiple comparisons. Two separate multivariate regression models are presented, one for predictors of calciphylaxis measured over the 12 months prior to diagnosis and the other for predictors at the time of diagnosis of calciphylaxis. The objective in doing so was to allow a comparison of the similarities and differences between the long-term risk factors for calciphylaxis to the risk factors present at the time of diagnosis. The covariates included in the multivariate models were chosen based on (1) the biological plausibility of an association with the occurrence of calciphylaxis, (2) the possibility that they may confound the relationship between the occurrence of calciphylaxis and another predictor of interest, and/or (3) the magnitude of their univariate relationship with the presence of calciphylaxis.

The Cox proportional hazards model was used to analyze the time from the diagnosis of calciphylaxis (or the corresponding time for controls) to death from any cause, with data censored on June 1, 2000, or if a patient became lost to follow-up prior to the end of study. The presence or absence of calciphylaxis, diabetic status, and the time spent on dialysis prior to the date of diagnosis of calciphylaxis were examined as risk factors for mortality. The univariate and multivariate survival model estimates, including relative risks, 95% confidence intervals, and *P* values to test association, are presented for the previously mentioned risk factors. Survival curves comparing patients with and without calciphylaxis are also presented.

RESULTS

Nineteen cases of calciphylaxis were identified. Fourteen patients had proximal lesions. Nine had distal lesions, and four had both proximal and distal lesions.

No penile lesions were identified. Six of seven patients evaluated (86%) had fine double lines on their x-rays, suggesting calcified small blood vessels. Of seven patients evaluated for hypercoagulable states, one had protein S deficiency (14%), and one had antiphospholipid antibodies (14%). Six patients were treated with a parathyroidectomy. Indications included severe pain despite analgesics (*N* = 6), nonhealing lesions (*N* = 4), and elevated iPTH levels (*N* = 5).

The characteristics of cases and controls over the 12 months prior to the diagnosis and at the time of diagnosis of calciphylaxis are shown in Tables 1 and 2. The two groups were similar with regard to age at the time of diagnosis of calciphylaxis, history of diabetes mellitus, and BMI at the time of diagnosis. The cases were more likely to be female and of Caucasian origin. The adjusted serum calcium levels were not significantly different between the two groups when compared at the time of diagnosis or as mean values over 12 months prior to the diagnosis. The cases had lower serum albumin levels, higher serum phosphate levels, and higher alkaline phosphatase levels compared with controls at the time of diagnosis and over the 12 months preceding the diagnosis of calciphylaxis. Although not statistically significant, there was a trend toward higher adjusted calcium-phosphate products and higher iPTH levels in the cases as compared with controls. The dosage of erythropoietin at the time of diagnosis of calciphylaxis was higher in the cases than the controls. The predialysis diastolic blood pressures at the time of diagnosis and over the preceding 12 months were similar for the two groups.

Table 3 shows the unadjusted risk of developing calciphylaxis associated with risk factors during the 12 months prior to the diagnosis of calciphylaxis. Each increment in serum albumin by 0.1 g/dL was associated with an approximately 25% lower likelihood of developing calciphylaxis (OR = 0.76, 95% CI, 0.64 to 0.94). A 2.7-fold higher risk of developing calciphylaxis was observed with each increment in serum phosphate level by 1 mg/dL (OR = 2.73, 95% CI, 1.28 to 5.78). An increased likelihood of developing calciphylaxis was associated with higher serum alkaline phosphatase levels (OR = 1.36, 95% CI, 1.01 to 1.83, respectively). There was a trend toward a higher risk of developing calciphylaxis with higher serum levels of iPTH over 12 months prior to diagnosis.

Table 3 also shows the unadjusted risk of developing calciphylaxis associated with risk factors at the time of diagnosis of calciphylaxis. The likelihood of developing calciphylaxis was sixfold higher in females compared with males (OR = 6.04, 95% CI, 1.62 to 22.6). Although not statistically significant, older patients showed a trend toward a lower relative risk of developing calciphylaxis. Each increment in serum albumin by 0.1 g/dL was associated with a 27% lower likelihood of developing calciphylaxis.

Table 1. Patient characteristics prior to diagnosis

Characteristic	Available cases	Controls (N = 54)	Cases (N = 19)
		Mean (SD) or % (N)	
Demographic data			
Age years	73	61.0 (15.5)	53.6 (11.6)
Female gender	73	39% (21)	79% (15) ^a
Race	73		
White		37% (20)	63% (12) ^a
Black		31% (17)	26% (5)
Other		31% (17)	11% (2)
Co-morbid conditions			
Presence of diabetes	73	39% (21)	42% (8)
Primary cause of ESRD	73		
Diabetes		37% (20)	42% (8)
Hypertension		13% (7)	5% (1)
Glomerulonephritis		22% (12)	11% (2)
Other		28% (15)	37% (7)
Duration of ESRD years	73	3.3 (2.8)	4.2 (4.6)
12-month average BP and laboratory measurements			
Pre-diastolic BP mm Hg	65	82.1 (10.8)	79.9 (11.7)
Post-diastolic BP mm Hg	65	77.9 (10.4)	74.2 (8.4)
Albumin g/dL	65	3.35 (.36)	2.88 (.49) ^a
Phosphate mg/dL	65	5.1 (1.3)	6.8 (1.7) ^a
Calcium mg/dL	65	9.13 (.71)	8.86 (1.32)
Calcium-phosphate product	65	46.5 (11.3)	60.8 (17.3)
iPTH pg/mL	60	312.5 (481.0)	359.2 (435.4)
Alkaline phosphatase IU/L	65	85.7 (40.8)	165.5 (180.4) ^a
Aluminum mg/dL	51	10.3 (18.1)	24.2 (26.3)
12-month cumulative medication doses			
Calcitriol µg	72	37.7 (59.6)	27.6 (53.8)
Erythropoietin per 1000 units	69	337.3 (336.1)	473.3 (411.1)
Iron dextran mg	71	2028.0 (4312.7)	1125.0 (1411.3)
Medications at diagnosis			
Warfarin		1 (1.8%)	7 (37%)
Prednisone		3	3
Calcitriol		3	4
Calcium salts		40 (69%)	14 (78%)

Abbreviations are: BP, blood pressure; ESRD, end-stage renal disease.

^aGroups were significantly different, $P < 0.01$ **Table 2.** Patient characteristics at the time of diagnosis

Characteristic	Available cases	Controls (N = 54)	Cases (N = 19)
		Mean (SD) or % (N)	
BP and laboratory measurements			
Pre-diastolic BP mm Hg	65	79.0 (13.2)	73.3 (18.0)
Post-diastolic BP mm Hg	65	75.0 (13.3)	71.5 (14.2)
BMI kg/m ²	67	24.6 (5.22)	25.9 (6.41)
Albumin g/dL	65	3.38 (.35)	2.62 (.73) ^a
Phosphate mg/dL	65	4.9 (1.7)	6.2 (1.8) ^a
Calcium mg/dL	65	9.15 (.74)	9.06 (1.09)
Calcium-phosphate product	65	44.1 (14.7)	56.1 (16.2)
iPTH pg/mL	60	283.0 (459.0)	420.0 (441.0)
Alkaline phosphatase IU/L	65	86.4 (47.8)	170.0 (132.3) ^a
Aluminum mg/dL	51	7.7 (8.0)	19.3 (23.5) ^a
Medication doses			
Calcitriol µg	72	0.68 (0.91)	0.61 (0.64)
Erythropoietin units	69	3979.4 (3792.2)	7539.0 (4498.6) ^a
Iron dextran mg	71	108.1 (145.4)	90.8 (151.7)

^aGroups were significantly different, $P < 0.01$

Table 3. Univariate conditional logistic model results for predictors measured over the 12 months prior to and at the time of diagnosis of calciphylaxis

Covariate	Odds of calciphylaxis			
	Measurements prior to diagnosis ^a		Measurements at the time of diagnosis	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographic data				
Age (1 year increase)	0.96 (0.92, 1.00)	0.070	0.96 (0.92, 1.00)	0.070
Female gender	6.04 (1.62, 22.6)	0.007	6.04 (1.62, 22.6)	0.007
Race		0.139		0.139
White	1.0		1.0	
Black	0.94 (0.15, 1.65)	0.250	0.94 (0.15, 1.65)	0.250
Other	0.18 (0.03, 1.03)	0.054	0.18 (0.03, 1.03)	0.054
Co-morbid conditions				
Diabetes (yes vs. no)	1.31 (0.40, 4.32)	0.655	1.31 (0.40, 4.32)	0.655
Primary cause of ESRD		0.424		0.424
Diabetes	1.0		1.0	
Hypertension	0.40 (0.04, 3.87)	0.430	0.40 (0.04, 3.87)	0.430
Glomerulonephritis	0.20 (0.02, 2.05)	0.175	0.20 (0.02, 2.05)	0.175
Polycystic kidney disease	0.60 (0.06, 6.12)	0.669	0.60 (0.06, 6.12)	0.669
Other	1.36 (0.35, 5.26)	0.659	1.36 (0.35, 5.26)	0.659
BP and laboratory measurements				
Pre-diastolic BP per mm Hg	0.98 (0.93, 1.04)	0.518	0.96 (0.92, 1.01)	0.154
Post-diastolic BP per mm Hg	0.97 (0.90, 1.03)	0.323	0.98 (0.93, 1.03)	0.441
BMI per kg/m ²	Not available		1.03 (0.93, 1.14)	0.518
Albumin per 0.1 g/dL	0.76 (0.64, 0.94)	0.011	0.73 (0.60, 0.89)	0.002
Phosphate per mg/dL	2.73 (1.28, 5.78)	0.009	1.85 (1.17, 2.93)	0.008
Calcium per mg/dL	0.49 (0.21, 1.15)	0.102	0.91 (0.50, 1.65)	0.748
Calcium-phosphate product	1.08 (1.01, 1.16)	0.017	1.06 (1.02, 1.11)	0.008
iPTH per 50 pg/mL	1.23 (0.97, 1.57)	0.088	1.02 (0.97, 1.09)	0.424
Alkaline phosphatase per 10 IU/L	1.36 (1.01, 1.83)	0.041	1.12 (1.02, 1.22)	0.012
Aluminum per mg/dL	1.02 (0.98, 1.07)	0.265	1.10 (0.98, 1.25)	0.115
Medication doses				
Calcitriol per µg	1.00 (0.99, 1.01)	0.625	0.94 (0.49, 1.80)	0.854
Erythropoietin per 500 units	1.00 (0.99, 1.00)	0.125	1.13 (1.04, 1.23)	0.005
Iron dextran per 50 mg	0.97 (0.93, 1.01)	0.129	0.93 (0.69, 1.25)	0.619

^aLaboratory measurements are averaged over the 12 months prior to diagnosis; medication doses are cumulative over the 12 months prior to diagnosis

laxis (OR = 0.73, 95% CI, 0.60 to 0.89). A 2.7-fold higher risk of developing calciphylaxis was observed with each increment in serum phosphate level by 1 mg/dL at the time of diagnosis of calciphylaxis (OR = 1.85, 95% CI, 1.17 to 2.93). An increased likelihood of developing calciphylaxis was associated with higher serum alkaline phosphatase levels (OR = 1.12, 95% CI, 1.02 to 1.22). A 13% increase in the risk of developing calciphylaxis was estimated for each 500 unit increment in erythropoietin dose at the time of diagnosis (OR = 1.13, 95% CI, 1.04 to 1.23). Higher dosages of calcitriol and iron dextran were not associated with the risk of developing calciphylaxis.

Table 4 illustrates the adjusted relative risk of developing calciphylaxis associated with potential risk factors at the time of diagnosis and for 12 months prior to the diagnosis of calciphylaxis in our final model. Female gender was independently associated with a fivefold to sevenfold higher risk of developing calciphylaxis (OR = 6.87, 95% CI, 0.50 to 94.7, and OR = 5.53, 95% CI, 0.53 to 57.3). Each increment in serum albumin level by 0.1 g/dL prior to diagnosis and at the time of diagnosis of calciphylaxis decreased the risk of developing calciphylaxis by

20% (OR = 0.79, 95% CI, 0.64 to 0.99, and OR = 0.80, 95% CI, 0.67 to 0.96). The risk of developing calciphylaxis was increased 3.5-fold for each 1 mg/dL increase in serum phosphate level over 12 months prior to diagnosis of calciphylaxis (OR = 3.51, 95% CI, 0.99 to 12.5). For each 10 IU/L increment in alkaline phosphatase at the time of diagnosis of calciphylaxis, there was a 19% increased risk of calciphylaxis (OR = 1.19, 95% CI, 1.00 to 1.40).

Eleven patients with calciphylaxis and seven controls died during the follow-up period. Seven out of 10 patients who died of complications related to calciphylaxis had proximal lesions. Infection of lesions was the major cause of death in six patients, and four of these patients had proximal lesions. One patient with calciphylaxis had bilateral breast lesions, and none of the cases had penile involvement. Calciphylaxis was complicated by infection of the lesions in 12 patients (63%).

Figure 1 illustrates the survival curves for cases and controls. The cases had an estimated one-year survival rate of 45% compared with 90% for the controls. The five-year survival was 35% for the cases and 60% for the controls. Table 5 shows the relative risk of death

Table 4. Multivariate conditional logistic model results for predictors measured over the 12 months prior to and at the time of diagnosis of calciphylaxis

Covariate	Odds of calciphylaxis			
	Measurements prior to diagnosis ^a		Measurements at the time of diagnosis	
	OR (95% CI)	P value	OR (95% CI)	P value
Female gender	5.53 (0.53, 57.3)	0.151	6.87 (0.50, 94.7)	0.150
Albumin per 0.1 g/dL	0.79 (0.64, 0.99)	0.037	0.80 (0.67, 0.96)	0.019
Phosphate per mg/dL	3.51 (0.99, 12.5)	0.052	Not included	
Alkaline phosphatase per 10 IU/L	Not included		1.19 (1.00, 1.40)	0.045

^aLaboratory measurements are averaged over the 12 months prior to diagnosis

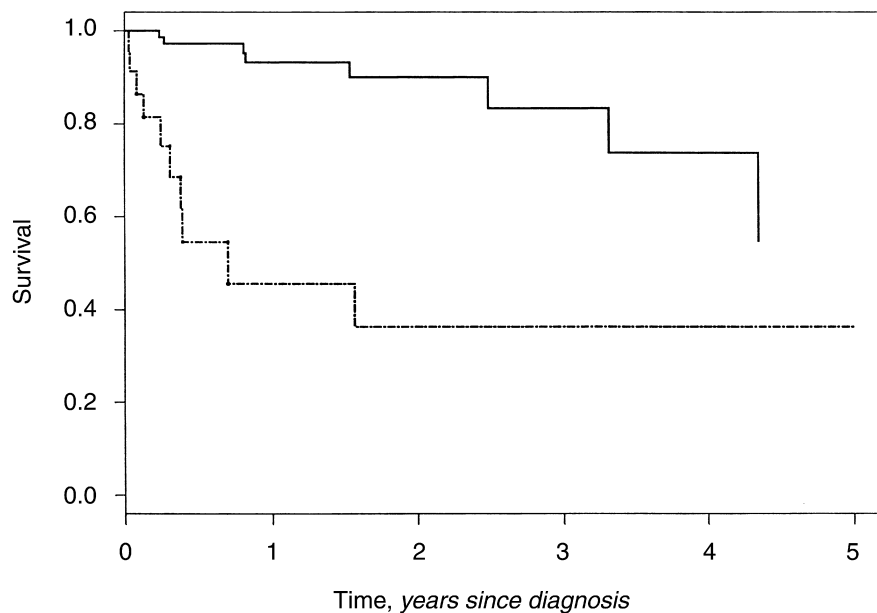


Fig. 1. Survivor curves comparing patients with calciphylaxis present (dotted line) to those without (solid line). Curve estimates were adjusted for the presence of diabetes and the duration of ESRD prior to diagnosis.

associated with calciphylaxis. The presence of calciphylaxis, diabetes mellitus, and longer duration of ESRD (hemodialysis) was independently associated with a higher risk of death. It was estimated that the presence of calciphylaxis increased the likelihood of death by eightfold compared with controls (RR = 8.58, 95% CI, 3.26 to 22.6). The likelihood of death was estimated to increase by fourfold in the presence of diabetes mellitus (RR = 3.97, 95% CI, 1.25 to 11.5) and by 21% for each year of ESRD therapy (RR = 1.21, 95% CI, 1.02 to 1.45).

DISCUSSION

This case control study identified risk factors for calciphylaxis, and to our knowledge we are the first to estimate the risk of death associated with the development of calciphylaxis. In the multivariate model, risk factors for developing calciphylaxis included female gender, low serum albumin, elevated serum phosphate, and higher serum alkaline phosphatase levels. In the univariate analysis, higher calcium phosphate products and higher doses

of erythropoietin were also associated with an increased risk of calciphylaxis.

Patients with calciphylaxis were at an eightfold increased risk of death compared with controls. The difference between survival curves of cases and controls in our study was most striking in the first year and more specifically in the first few months after the diagnosis of calciphylaxis. This observation is consistent with the rapid disease progression associated with calciphylaxis. Consistent with previous studies, the major cause of death among patients with calciphylaxis was infection [5]. The majority of cases who died had proximal lesions. Proximal lesions have been observed to be associated with worse outcomes in previous studies [1, 5]. The increased risk of death among patients with calciphylaxis may be due to factors predisposing patients to calciphylaxis such as malnutrition or complications associated with the development of calciphylaxis, including infection and sepsis.

Consistent with previous reports, we have demon-

Table 5. Cox regression results modeling time from diagnosis to all-cause mortality

Covariate	Deaths (N = 19)	Mortality rate per 100 years	Unadjusted		Adjusted ^a	
			RR (95% C.I.)	P value	RR (95% C.I.)	P value
Presence of calciphylaxis						
No	8	7.0	1.0		1.0	
Yes	11	57.5	7.29 (2.88, 18.5)	<0.001	8.58 (3.26, 22.6)	<0.001
Presence of diabetes						
No	10	10.0	1.0		1.0	
Yes	9	30.0	2.13 (0.81, 5.61)	0.127	3.97 (1.25, 11.5)	0.018
Duration of ESRD years			1.13 (0.96, 1.37)	0.152	1.21 (1.02, 1.45)	0.032

^a Adjusted for presence of calciphylaxis, diabetes, and duration of ESRD

strated a higher risk of calciphylaxis among females [1, 4]. The relatively larger proportion of adipose tissue in females compared with males may predispose to relative hypoperfusion of the skin and subcutaneous tissue. Alternatively, a relative increase in the subcutaneous tissue may increase tensile stress on the septa connecting the skin to the deep fascia and on arterioles resulting in cutaneous hypoperfusion, and ischemic necrosis [8]. The predominant occurrence of lesions of calciphylaxis in locations where adipose tissue is more abundant in the current and previous studies, and previously reported associations between obesity and calciphylaxis support this hypothesis [4, 9]. However, the majority of cases and controls in the current study were not obese (median BMI 24 to 25), suggesting that obesity is not a prerequisite for the development of calciphylaxis.

Our study demonstrated a higher risk of calciphylaxis among Caucasian patients. This is consistent with several studies that have reported a preponderance of Caucasians among patients with calciphylaxis [1, 3–5]. All patients with calciphylaxis were Caucasian in the study reported by Bleyer et al, despite an overall prevalence of 50% African Americans in their hemodialysis population [4]. Some investigators have suggested relative difficulty in diagnosing skin lesions of calciphylaxis in patients with darker skin as one possible explanation for this observation, although other factors likely confer protection to non-Caucasian populations from developing calciphylaxis [4].

The increased risk of developing calciphylaxis associated with lower levels of serum albumin relative to controls has been reported previously [4]. Bleyer et al reported a 17-fold increase in the risk of developing calciphylaxis with each decrease in albumin by 1 g/L (OR = 16.9, 95% CI, 5.25 to 54.5). This finding is supported by Coates et al, who reported a loss of >10% body weight over six months preceding the diagnosis of calciphylaxis in 7 out of 16 patients in their series [2]. Low albumin is associated with poor wound healing and an increased risk of infection [10, 11], suggesting that low albumin may predispose patients to calciphylaxis.

The association of calciphylaxis with parameters of

calcium-phosphate metabolism has been variable in previous studies. We have demonstrated an increased risk of calciphylaxis among patients with elevated phosphate prior to diagnosis and elevated alkaline phosphate at the time of diagnosis. In addition, we found a trend toward higher adjusted calcium-phosphate products and lower serum calcium levels among patients with calciphylaxis. We demonstrated a threefold increase in the likelihood of developing calciphylaxis for each increment in serum phosphate by 1 mg/dL over the 12 months prior to the diagnosis of calciphylaxis and a 19% increased risk of developing calciphylaxis associated with each 10 IU/L increase in alkaline phosphatase at the time of diagnosis and a trend toward higher iPTH levels in the cases. This confirms previous reports of higher serum phosphate and higher serum levels of alkaline phosphatase [3, 4, 6]. Angelis et al reported median phosphate levels of 8.2 and 5.7 for calciphylaxis cases and controls, respectively ($P = 0.001$) [3]. The higher levels of alkaline phosphatase may be indicative of more advanced bone disease, particularly in the setting of relatively severe hyperparathyroidism in several patients with ESRD who develop calciphylaxis. The relatively lower levels of serum calcium in the cases may result from precipitation of calcium with phosphate in blood vessels and other sites in the setting of elevated phosphate levels and elevated calcium-phosphate products. There was a trend toward an increased risk of developing calciphylaxis with higher levels of parathyroid hormone in our study. The association of calciphylaxis with elevated parathyroid hormone levels and elevated calcium-phosphate products has been inconsistent in previous reports. These differences may be a reflection of the small sample size and limited statistical power to identify associations and of the multifactorial etiology of the condition [1–6]. Similarly, some reports have suggested a benefit of parathyroidectomy. Other studies have not shown a benefit from parathyroidectomy, suggesting a multifactorial etiology of this condition [12–14]. Our sample size was too limited to make any conclusions about the utility of parathyroidectomy, and there are no prospective studies to confirm or refute previous reports.

Consistent with previous reports, we discovered a trend toward a higher risk of calciphylaxis in younger hemodialysis patients. A longer exposure to renal replacement therapy in younger patients with ESRD may increase the likelihood of developing calciphylaxis by increasing the exposure time to factors that predispose to calciphylaxis [3, 15]. In contrast to some reports [4], diabetes was not a risk factor for calciphylaxis. A possible explanation for this difference is the smaller proportion of obese diabetic patients in our study.

Studies have reported associations between iron dextran, vitamin D preparations, and calcium-containing phosphate binding agents and calciphylaxis (abstract, Braden et al, *J Am Soc Nephrol* 8:549, 1997) [16]. In the univariate analysis, we found that patients with calciphylaxis had been receiving higher doses of erythropoietin and there was a trend toward lower doses of iron dextran compared with controls. Zacharias et al reported an association between iron intake and the risk of developing calciphylaxis [16]. These findings may reflect more severe anemia and inadequate iron replacement in cases. This could theoretically contribute to impaired cutaneous perfusion and oxygen delivery, thereby increasing the risk of skin necrosis. Although not statistically significant, the use of calcium salts was more prevalent in cases compared to controls in the current study. This is consistent with Zacharias et al, who reported an association between the use of calcium salts at one and two to three months and the risk of developing calciphylaxis in a case control study (per 1 g calcium ingested; OR = 1.029, $P = 0.056$, and OR = 1.011, $P = 0.057$) [16]. The chronic use of calcium salts may contribute to a higher risk of calcium-phosphate precipitation in the tissues.

The major limitation of our study is a relatively small sample size, which limits power to detect associations. The laboratory parameters, blood pressure, and medication dosage were measured at the time of diagnosis of calciphylaxis and over a 12-month period prior to diagnosis. The associations detected between some of these parameters and the risk of developing calciphylaxis could be considered stronger and more likely to be causal if there was better understanding of the course of development of calciphylaxis (acute, subacute, or chronic). Prospective studies are needed to define these associations better. Despite limitations, this is the largest controlled study on calciphylaxis to date, and is the first study to simultaneously estimate the magnitude of risk associated with postulated risk factors and the risk of death associated with calciphylaxis.

In summary, calciphylaxis is associated with very high mortality. The strongest predictors of developing calciphylaxis in this study include female gender, low serum albumin, elevated serum phosphate, and elevated serum alkaline phosphatase levels. Based on these observa-

tions, a strict control of serum phosphate with dietary phosphate restriction and phosphate-binding agents in high-risk patients appears to be important [17, 18]. Maintaining adequate nutrition may also be important in preventing the development of calciphylaxis. Early and aggressive treatment of infections complicating lesions of calciphylaxis, a lower calcium concentration in the dialysate [19, 20], and avoidance of high calcium-phosphate products in patients with impaired renal function may reduce morbidity and mortality associated with calciphylaxis. Prospective controlled multicenter trials would greatly aid in a better understanding of risk factors for calciphylaxis and in the prevention and management of this condition.

ACKNOWLEDGMENTS

This study was supported by a PHS grant from the National Institute of Health, Bethesda, MD (DK07721-06) and a Veterans Administration career development award. We thank Ms. Linda Jackson at Northwest Kidney Center (Seattle, WA, USA) for her invaluable assistance in abstracting data.

Reprint requests to Catherine Stehman-Breen M.D., Division of Nephrology, VA Puget Sound Health Care System, Mailstop 111A, Seattle, Washington 98108, USA.
E-mail: cos@u.washington.edu

REFERENCES

- HAFNER J, KEUSCH G, WHAL C, et al: Uremic small-artery disease with medial calcification and intimal hyperplasia (so-called calciphylaxis): A complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol* 33:954-962, 1995
- COATES T, KIRKLAND G, DYMCK R, et al: Cutaneous necrosis from calcific uremic arteriopathy. *Am J Kidney Dis* 32:384-391, 1998
- ANGELIS M, WONG L, MYERS S, WONG L: Calciphylaxis in patients on hemodialysis: A prevalence study. *Surgery* 122:1083-1090, 1997
- BLEYER A, CHOI M, IGWEMEZIE B, et al: A case control study of proximal calciphylaxis. *Am J Kidney Dis* 32:376-383, 1998
- HAFNER J, KEUSCH G, WAHL C, BURG G: Calciphylaxis: A syndrome of skin necrosis and acral gangrene in chronic renal failure. *Vasa* 27:137-143, 1998
- GIPSTEIN R, COBURN J, ADAMS D, LEE D, et al: Calciphylaxis in man. *Arch Intern Med* 136:1273-1280, 1976
- SELYE H, GABBIANI G, STREBEL R: Sensitization to calciphylaxis by endogenous parathyroid hormone. *Endocrinology* 554-558, 1962
- OH D, EULAU D, TOKUGAWA D, MCGUIRE J, et al: Five cases of calciphylaxis and a review of literature. *J Am Acad Dermatol* 40:979-987, 1999
- RUGGIAN J, MAESAKA J, FISHBANE S: Proximal calciphylaxis in four insulin-requiring diabetic hemodialysis patients. *Am J Kidney Dis* 28:409-414, 1996
- POWE N, JAAR B, FURTH S, HERMANN J, et al: Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int* 55:1081-1090, 1999
- KAY S, MORELAND J, SCHMITTER E: Nutritional status and wound healing in lower extremity amputations. *Clin Orthop* 217:253-256, 1987
- ANDROGUE H, FRAZIER M, ZELUFF B, SUKI W: Systemic calciphylaxis: Successful treatment with parathyroidectomy. *J Urol* 129:362-363, 1983

13. BUDISAVJEVIC M, CHIK D, PLOTH D: Calciphylaxis in chronic renal failure. *J Am Soc Nephrol* 7:978–982, 1996
14. CHAN Y, MAHONEY J, TURNER J, POSEN S: The vascular lesions associated with skin necrosis in renal disease. *Br J Dermatol* 109:85–95, 1983
15. BYRNE C, VERNON P, COHEN J: Effect of age and diagnosis on survival of older patients beginning chronic dialysis. *JAMA* 271:34–36, 1994
16. ZACHARIAS J, FONTAINE B, FINE A: Calcium use increases risk of calciphylaxis: A case-control study. *Perit Dial Int* 19:248–252, 1999
17. McAULEY K, DEVEREUX F, WALKER R: Calciphylaxis in two non-compliant patients with end-stage renal failure. *Nephrol Dial Transplant* 12:1061–1063, 1997
18. RICHENS G, PIEPKORA M, KRUEGE G: Calcifying panniculitis associated with renal failure. *J Am Acad Dermatol* 6:537–539, 1982
19. MASSRY S, COBURN J, HARTENBOWER D: The effect of calcemic disorders and uremia on the mineral content of the skin. *Israel J Med Sci* 7:514–517, 1971
20. FERNANDEZ E, MONTOLIU J: Successful treatment of massive uremic tumoral calcinosis with daily hemodialysis and very low calcium dialysate. *Nephrol Dial Transplant* 9:1207–1209, 1994