Characterization of Risk Factors for Calciphylaxis in Hemodialysis Patients in the Fraser Health Renal Program – A Matched Case-Control Retrospective Review

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Background

- Calciphylaxis (CUA) is a lethal and rare disease characterized by ischemic and necrotic skin lesions caused by vascular calcification of adipose tissue[1]:
  - Many non-modifiable and modifiable risk factors
  - Occurs predominantly in end-stage renal disease population
  - Pathogenesis not well understood and treatment options limited due to lack of interventional studies
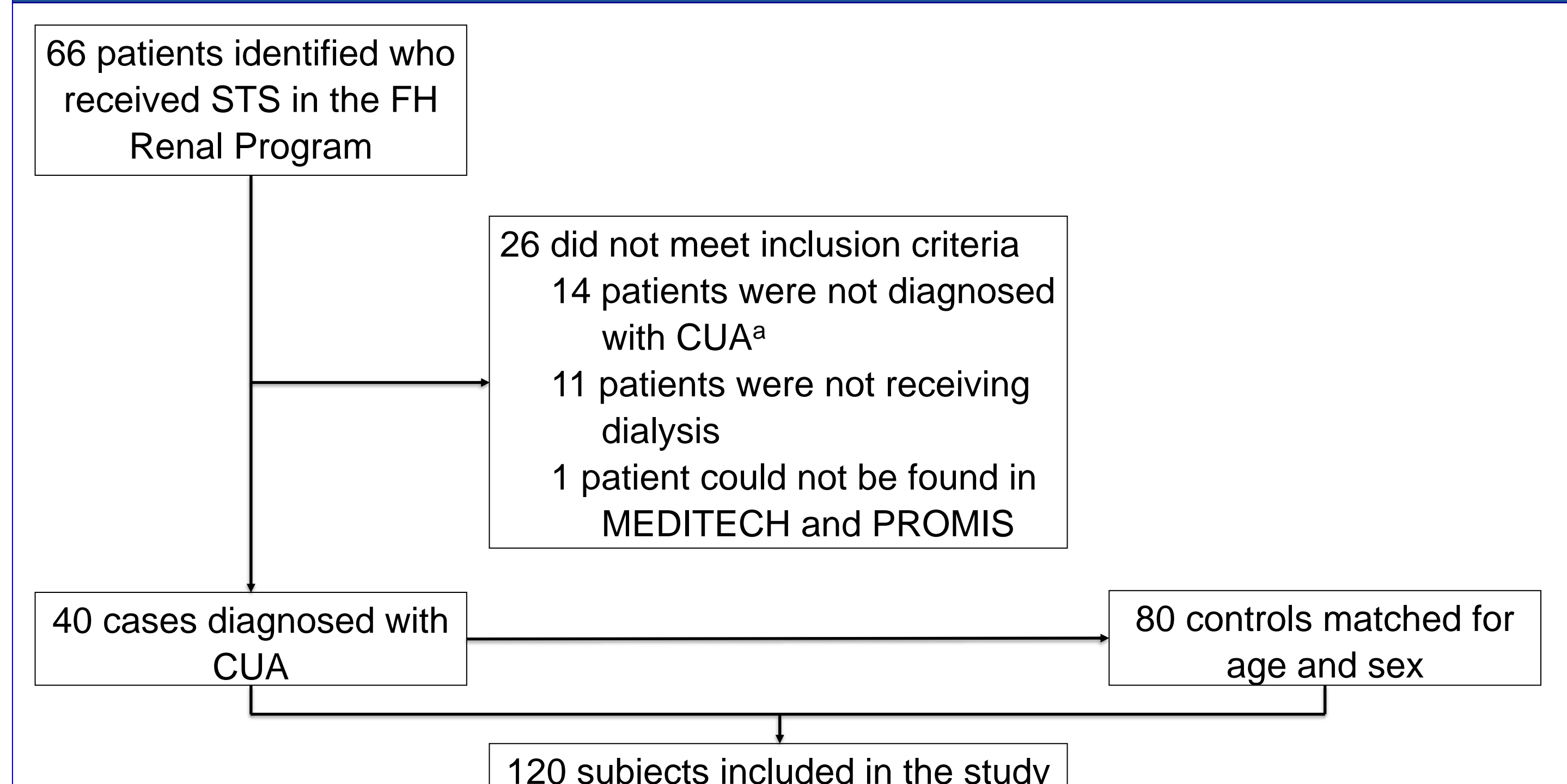
Objectives

- **Primary:** Describe risk factors for CUA in hemodialysis patients
- **Secondary:** Determine prevalence, incidence, and outcomes of patients diagnosed with CUA

Methods

- **Design:** Retrospective matched 1:2 case-control study of hemodialysis patients diagnosed with and without CUA
- **Study Period:** September 2, 2017 to July 3, 2020
- **Patient Population:** ≥18 years of age; chronic hemodialysis patients in Fraser Health (FH) Renal Program; cases received ≥1 dose of sodium thiosulfate (STS) for treatment of CUA

Results

Figure 1. Flow Chart of Identified Cases and Controls Included in the Study

66 patients identified who received STS in the FH Renal Program

26 did not meet inclusion criteria
14 patients were not diagnosed with CUA[a]
11 patients were not receiving dialysis
1 patient could not be found in MEDITECH and PROMIS

40 cases diagnosed with CUA

80 controls matched for age and sex

120 subjects included in the study

[a]Patients either had STS added to their medication profile in error and/or did not have any mention of CUA in their electronic patient records.

Table 1. Baseline Characteristics of Cases and Controls at Diagnosis

Characteristic	Cases (n=40)	Controls (n=80)	p-value
Demographics			
Age, years	68 (45-85)	68 (45-85)	Not applicable
M/F, no. (%)	12 (30)/28 (70)	24 (30)/56 (70)	Not applicable
HD[a], no. (%)	26 (65)	72 (90)	0.001
PD[a], no. (%)	15 (37.5)	8 (10)	<0.001
Dialysis vintage, days	895 (0-7833)	841 (15-9429)	0.96
BMI, kg/m^2	30.1 (14.7-60.9)	26.6 (16-43.8)	0.002
DM, no. (%)	31 (77.5)	56 (70)	0.39
Lab parameters			
A1C, %	7 (4-9.4)	6.8 (4.1-14.9)	0.45
Serum Ca, mmol/L	2.2 (1.7-2.6)	2.2 (1.7-2.9)	0.22
Serum PO$_4$, mmol/L	1.5 (0.7-2.6)	1.6 (0.9-3.1)	0.57
Serum PTH, pmol/L	43.4 (3.7-291.3)	40 (0.8-228.3)	0.28
Hb, g/L	96 (68-130)	107 (66-144)	0.01
Serum ferritin, µg/L	658.5 (32-1902)	764.5 (23-1913)	0.26
Serum Fe, µmol/L	7 (1-18)	10 (3-32)	<0.001
TSAT, %	21 (4-58)	27 (8-71)	0.001
Medications			
Calcium, no. (%)	34 (85)	63 (78.8)	0.41
Sevelamer, no. (%)	15 (37.5)	7 (8.8)	<0.001
Lanthanum, no. (%)	2 (5)	1 (1.3)	0.22
Cinacalcet, no. (%)	8 (20)	4 (5)	0.01
Vitamin D, no. (%)	9 (22.5)	14 (17.5)	0.51
Alfacalcidol, no. (%)	22 (55)	46 (57.5)	0.79
Calcitriol, no. (%)	6 (15)	10 (12.5)	0.70
Warfarin, no. (%)	21 (52.5)	8 (10)	<0.001
Iron (IV), no. (%)	24 (60)	63 (78.8)	0.03
Iron (PO), no. (%)	14 (35)	14 (17.5)	0.03
Insulin, no. (%)	29 (72.5)	39 (48.8)	0.01
Corticosteroids, no. (%)	10 (25)	13 (16.3)	0.25

M=male; F=female; HD=hemodialysis; PD=peritoneal dialysis; BMI=body mass index; DM=diabetes; A1C=glycated hemoglobin; Ca=calcium; PO$_4$=phosphate; PTH=parathyroid hormone; Hb=hemoglobin; Fe=iron; TSAT=transferrin saturation
[a]One patient was receiving hybrid HD/PD at the time of diagnosis.

Table 2. Univariate Logistic Regression Analysis of CUA Risk Factors at Diagnosis[a]

	OR (95% CI)	p-value
Demographics		
HD	0.17 (0.06-0.53)	0.002
PD	6.31 (2.06-19.33)	0.001
BMI	1.08 (1.02-1.14)	0.007
Lab parameters		
Hb	0.97 (0.94-1.00)	0.02
Serum Fe	0.81 (0.72-0.91)	<0.001
TSAT	0.001 (0-0.12)	0.005
Medications		
Sevelamer	6.46 (2.12-19.69)	0.001
Cinacalcet	4.00 (1.21-13.28)	0.02
Warfarin	9.29 (3.16-27.30)	<0.001
Iron (IV)	0.40 (0.17-0.94)	0.04
Iron (PO)	3.23 (1.18-8.87)	0.02
Insulin	2.70 (1.19-6.11)	0.02

OR=odds ratio; CI=confidence interval; HD=hemodialysis; PD=peritoneal dialysis; BMI=body mass index; Hb=hemoglobin; Fe=iron; TSAT=transferrin saturation
[a]Dialysis vintage, diabetes, glycated hemoglobin, serum calcium, serum phosphate, serum parathyroid hormone, serum ferritin, calcium, lanthanum, vitamin D, alfacalcidol, calcitriol, and corticosteroids were not statistically significant (p≥0.05).

Table 3. Multivariate Logistic Regression Analysis of CUA Risk Factors at Diagnosis

	OR (95% CI)	p-value
Demographics		
PD	6.57 (1.36-31.79)	0.02
Lab parameters		
Serum Fe	0.79 (0.66-0.96)	0.02
Medications		
Sevelamer	8.60 (1.23-60.08)	0.03
Warfarin	5.12 (1.25-20.93)	0.02

OR=odds ratio; CI=confidence interval; PD=peritoneal dialysis; Fe=iron

Table 4. Prevalence, Incidence, and Outcomes of CUA

Prevalence and Incidence	Prevalence[a]	Incidence Rate
Cases	40/2057 (1.9)	6.9 per 1000 person-years

Outcomes	Cases (n=40)	Controls (n=80)
Recoveries, no. (%)	11 (27.5)	-
Still receiving treatment, no. (%)	2 (5)	-
All-cause mortality, no. (%)	27 (67.5)	24 (30)
At 6 months, no. (%)	19 (47.5)	5 (6.3)
At 12 months, no. (%)	23 (57.5)	12 (15)
Time to death, days (range)	78 (0-1399)	367 (0-977)

[a]Number of cases/total number of chronic hemodialysis patients during the study period (%).

Limitations

- Retrospective analysis
- Small sample size
- CUA cases identified if they received STS
- Risk factors collected at diagnosis
- Duration and adherence of medications unknown
- Medication history limited by MEDITECH and PROMIS accessibility

Conclusion

- CUA predominantly identified in older females with obesity consistent with literature[1]; however, lab parameters not especially abnormal in patients with CUA at diagnosis
- Peritoneal dialysis, serum iron, sevelamer, and warfarin identified as significant and strong risk factors associated with CUA
- Low prevalence of 1.9% and high mortality of 57.5% at 12 months for CUA similar to other studies[2,3]
- Future studies should further investigate impact of minimizing exposure to additional risk factors such as dialysis modality, anemia, mineral bone abnormalities, and vitamin K antagonism or deficiency in CUA development

References
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