Calciphylaxis

From basic mechanisms to clinical management

Dr. Rachel M. Holden
Cutaneous Molt Induced by Calciphylaxis in the Rat
Author(s): Hans Selye, G. Gentile and P. Piorescchi

Calciphylaxis is a condition of induced systemic hypersensitivity in which, during a “critical period” after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone, sodium sulfathiazole), treatment with certain challengers (for example, metallic salts, albumen) causes an acute local calcification, followed by inflammation and sclerosis. The term was coined in
Calciphylaxis - definition

- Rare, life-threatening disorder characterized by:

  Occlusion of micro vessels in the subcutaneous adipose tissue and dermis leading to intensely painful, ischemic skin lesions
Violaceous patch

Sub-cutaneous nodule

Erythema

Induration with dusky discoloration

Multiple plaques

Necrotic ulcer with eschar
How do we describe calciphylaxis?

• Uremic versus non-uremic

• Central versus Peripheral

  Central: central areas within subcutaneous tissue such as abdomen, thighs or breasts

  Peripheral: peripheral sites with limited adipose tissue such as shins or digits

• Ulcerated lesions versus non-ulcerated lesions
Two cases

- Patient A - 2004
- Patient B - 2016

Central calciphylaxis

Peripheral calciphylaxis
Patient A – central calciphylaxis

- 42 year old female
- Over weight
- ESKD secondary to FSGS
- Type 2 DM on regular insulin injections
- Peritoneal dialysis x 3 yrs
- Presented April, 2004
Patient A: CKD-MBD parameters

<table>
<thead>
<tr>
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<tr>
<td>6Apr01 1352</td>
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<tr>
<td>3Aug01 1325</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>6Mar03 1043</td>
<td></td>
<td>2.45!</td>
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</tr>
<tr>
<td>9May03 1105</td>
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<td>2.08!</td>
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<td>1Aug03 1100</td>
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<td>7Apr04 1830</td>
<td>2.52</td>
<td>0.84</td>
<td>2.57!</td>
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Takes calcium binders – 1000 elemental calcium TID

calciphylaxis diagnosed
Patient A: CKD-MBD parameters

<table>
<thead>
<tr>
<th>Date/Time</th>
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<tr>
<td>20May04 1324</td>
<td>4.9</td>
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calciphylaxis diagnosed
Patient A

FINAL DIAGNOSIS

SUBCUTANEOUS TISSUE, ABDOMINAL WALL, DEBRIDEMENT PROCEDURE

: FAT NECROSIS, ACUTE INFLAMMATION (? ABSCESS) WITH DYSTROPHIC CALCIFICATION
Patient B – peripheral calciphylaxis

• 55 year old male
• Low BMI
• ESKD secondary to hypertension
• Kidney transplant 1991
• Baseline creatinine ~ 180 umol/L
• Presented May, 2016
Patient B CKD-MBD parameters

<table>
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</tr>
</thead>
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<td>2.10</td>
<td>0.66</td>
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<td>16Dec15 0756</td>
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<td>31Mar16 0950</td>
<td>2.06</td>
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<td>15Apr16 0040</td>
<td>1.95</td>
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<td>09May16 1230</td>
<td>2.05</td>
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<td>0.87</td>
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Warfarin started for AF
Calcitriol started
calciphylaxis diagnosed
FINAL DIAGNOSIS

SKIN, PUNCH BIOPSY, ANTERIOR RIGHT SHIN:
    : PERIVASCULAR CALCIUM STIPPLING CONSISTENT WITH CALCIPHYLAXIS (SEE COMMENT).

DIAGNOSIS COMMENT
The HandE stained sections show edema with sparse superficial interstitial neutrophilic, lymphocytic and eosinophilic inflammatory infiltrate. Von Kossa special stain shows small deep vessels with calcium stippling of the vessel walls. Taken together with the clinical history, this finding is consistent with calciphylaxis.
Calciphylaxis - Epidemiology

- 35/10,000 patients undergoing HD in the US
- 4/10,000 in Germany
- <1/10,000 in Japan
- Interval between dialysis onset and disease ranges from 30 months in the US and Germany to 105 months in Japan
- Higher incidence in peritoneal dialysis patients
- Unknown incidence in KT recipients
Calciphylaxis – who is at risk?

A Nationally Representative Study of Calcific Uremic Arteriolopathy Risk Factors

Sagar U. Nigwekar,* Sophia Zhao,* Julia Wenger,† Jeffrey L. Hymes,‡ Franklin W. Maddux,‡ Ravi I. Thadhani,* and Kevin E. Chan*‡

## Who is at risk?

### Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=1030)</th>
<th>Controls (n=2060)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Comorbidities and vital signs</strong></td>
<td></td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>61</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>65</td>
<td>42</td>
<td>&lt;0.001</td>
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<tr>
<td>Weight, kg</td>
<td>101.2±29.3</td>
<td>82.0±25.5</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI, kg/m²</td>
<td>36.7±10.2</td>
<td>30.3±8.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>150±31</td>
<td>148±27</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>78±18</td>
<td>78±17</td>
<td>0.66</td>
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</table>

## Who is at risk?

**CKD-MBD parameters + treatments**

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<tr>
<th>Characteristic</th>
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<th>P Value</th>
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<tbody>
<tr>
<td><strong>Mineral bone parameters and therapies</strong></td>
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<tr>
<td>Serum calcium (albumin corrected), mg/dl</td>
<td>9.1±0.8</td>
<td>9.0±0.8</td>
<td>0.04</td>
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<tr>
<td>Serum phosphorus, mg/dl</td>
<td>4.9±2.3</td>
<td>4.6±2.0</td>
<td>0.001</td>
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<tr>
<td>Serum PTH, pg/ml</td>
<td>379 (184, 651)</td>
<td>250 (100, 471)</td>
<td>&lt;0.001</td>
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<td>Serum ALP, U/L</td>
<td>116.6±87.5</td>
<td>106.8±74.3</td>
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<td>Serum 25-hydroxyvitamin D, ng/ml</td>
<td>19.4±10.1</td>
<td>16.7±11.2</td>
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<td>Dialysate calcium, mmol/L</td>
<td>2.5±0.3</td>
<td>2.5±0.2</td>
<td>0.20</td>
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<td><strong>Nutritional vitamin D treatment, %</strong></td>
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<td>5</td>
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<td>Activated vitamin D treatment, %</td>
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<td>Cinacalcet treatment, %</td>
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<td>Phosphate-binding agent treatment, %</td>
<td>35</td>
<td>31</td>
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## Who is at risk?
### Other medications

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<tr>
<td>Serum albumin, g/dl</td>
<td>3.5±0.5</td>
<td>3.5±0.6</td>
<td>0.49</td>
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<tr>
<td>Hemoglobin, g/dl</td>
<td>10.2±1.5</td>
<td>10.4±1.5</td>
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<td>Serum bicarbonate, mEq/L</td>
<td>22.5±3.9</td>
<td>22.5±4.0</td>
<td>0.61</td>
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<tr>
<td>sPKtV</td>
<td>1.5±0.4</td>
<td>1.6±0.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Warfarin treatment, %</td>
<td>14</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin treatment, %</td>
<td>25</td>
<td>22</td>
<td>0.04</td>
</tr>
<tr>
<td>ESA treatment, %</td>
<td>45</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEi/ARB treatment, %</td>
<td>15</td>
<td>13</td>
<td>0.22</td>
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</table>

Diagnosis

• Clinical suspicion
  – Derangements in CKD-MBD parameters often present but not necessarily so
  – German registry data
    – 86% of calciphylaxis patients had either normal or low calcium
    – 40% had either normal or low phosphate
<table>
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<th>Table 2. Differential Diagnosis of Calciphylaxis.</th>
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<tr>
<td>Warfarin-induced skin necrosis</td>
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<td>Atherosclerotic vascular disease</td>
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<td>Cellulitis</td>
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<td>Cholesterol embolization</td>
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<tr>
<td>Dystrophic calcinosis cutis</td>
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<tr>
<td>Livedoid vasculopathy</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
</tr>
<tr>
<td>Oxalosis</td>
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<tr>
<td>Pyoderma gangrenosum</td>
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<tr>
<td>Purpura fulminans</td>
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<tr>
<td>Necrotizing vasculitis</td>
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<tr>
<td>Martorell’s ulcer</td>
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What is the pathology of calciphylaxis?

Classic histologic features

• Calcification
• Fibrointimal hyperplasia
• Thrombosis
Calcification

- Active cell-mediated process
- Depends on balance between promoters and inhibitors
- Adipocytes, vascular smooth muscle cells and osteoblasts share common mesenchymal origin
Vascular calcification – an active, cell-mediated process

Mechanisms of micro-vessel calcification

Phosphate uptake by PiT-1 and PiT-2

VSMCs

Calcifying VSMCs
Mechanisms of micro-vessel calcification

Phosphate uptake by PiT-1 and PiT-2

VSMCs

Runx2

Calcifying VSMCs
Mechanisms of micro-vessel calcification

Osteoblastic Transdifferentiation

- Osteoblasts are bone forming cells
- Secrete bone matrix proteins

Phosphate uptake by PiT-1 and PiT-2

VSMCs
Mechanisms of micro-vessel calcification

Phosphate uptake by PiT-1 and PiT-2

Osteoblastic Transdifferentiation

**Nidus Formation**
- Apoptotic Bodies
- Elastin matrix Degradation
- Matrix Vesicles

VSMCs

Figure 1.1 Mechanism of vascular calcification. The balance between phosphate uptake inhibitors and promoter is tipped towards inducing the promoters of calcification, thus accelerating the process.
Mechanisms of micro-vessel Calcification

Phosphate uptake by PiT-1 and PiT-2

- Osteoblastic Transdifferentiation
- Nidus Formation

Promoters of Vascular Calcification
- Phosphate
- Calcium

VSMCs
Mechanisms of micro-vessel Calcification

Phosphate uptake by PiT-1 and PiT-2

VSMCs

Osteoblastic Transdifferentiation

Nidus Formation

Promoters of Vascular Calcification

Inhibitors of Vascular Calcification
- Matrix Gla Protein
- Fetuin-A
- Magnesium
Mechanisms of Vascular Calcification

Phosphate uptake by PiT-1 and PiT-2

VSMCs

Osteoblastic Transdifferentiation

Nidus Formation

Inhibitors of Vascular Calcification

Promoters of Vascular Calcification

Tissue-Specific Mechanisms

Calcifying VSMCs

Figure 1.1 Mechanism of vascular calcification. Phosphate uptake by PiT-1 and PiT-2 promotes calcification. The presence of inhibitors and promoter is tipped towards inducing the promoters of calcification, thus accelerating the process. (Ref. 50)
Calcification in arterioles in clinical calciphylaxis

Calcification in arteriole

Up-regulation of Runx2

Calciphylaxis – osteogenic phenotype

Adipocytes calcify in calciphylaxis

Calcification of adipocytes

BMP-2 staining of adipocytes
Obesity

Adipocyte induced arterial calcification is prevented with sodium thiosulfate

Neal X. Chen\textsuperscript{a,*}, Kalisha O’Neill\textsuperscript{a}, Nader Kassis Akl\textsuperscript{a}, Sharon M. Moe\textsuperscript{a,b}

\textsuperscript{a} Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA
\textsuperscript{b} Roudebush VA Medical Center, Indianapolis, IN, USA
Adipocytes express the ‘osteogenic program’
Mature adipocytes exposed to high phosphate media calcify
Adipocytes enhance calcification of VSMCs
Pathology of calciphylaxis

Histologic features

• Calcification
• Fibrointimal hyperplasia
• Thrombosis
How specific are these histologic findings for calciphylaxis?

Questionable specificity of histologic findings in calcific uremic arteriolopathy

Carla L. Ellis¹ and W. Charles O'Neill²

¹Department of Pathology, Emory University School of Medicine, Atlanta, Georgia, USA; and ²Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA
## Table 1 | Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Amputations</th>
<th>Skin biopsies</th>
<th>P Value</th>
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<tbody>
<tr>
<td>N</td>
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<td>37</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SEM)</td>
<td>62 ± 1.9</td>
<td>53 ± 2.5</td>
<td>0.006</td>
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<tr>
<td>Gender (% female)</td>
<td>29</td>
<td>81</td>
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<tr>
<td>Diabetes (%)</td>
<td>71</td>
<td>51</td>
<td>0.14</td>
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<tr>
<td>ESRD (%)</td>
<td>100</td>
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<td>0.005</td>
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<tr>
<td>Dialysis</td>
<td>91</td>
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<td>Transplantation</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Warfarin use (%)</td>
<td>21</td>
<td>49</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease.
How specific is a finding of vascular calcification in a skin biopsy?

Healthy skin in patient with ESKD

Suspected calciphylaxis

Prevalence of VK positive calcification was similar between skin biopsies performed for suspicion of calciphylaxis and healthy skin from amputation margins.
How specific is a finding of calcification of the subcutaneous fat in a skin biopsy?

Healthy skin in patient with ESKD

Suspected calciphylaxis

Prevalence of extravascular soft tissue calcification was not different
How specific is a finding of intimal hyperplasia in a skin biopsy?

Healthy skin in patient with ESKD

Suspected calciphylaxis

Prevalence of intimal hyperplasia was low in both groups
How specific is a finding of arterial thrombosis in a skin biopsy?

Healthy skin in patient with ESKD

Suspected calciphylaxis

Only the presence of thrombosis was significantly different between the two groups and only in ‘high clinical suspicion biopsies’
Summary: pathology

• Histologic changes in small arteries and arterioles of skin and subcutaneous tissues ascribed to calciphylaxis can occur in patients with ESKD without clinical evidence of calciphylaxis.

• Combination of calcification and thrombosis may be important – more prevalent in high-suspicion skin biopsies than in amputation specimens.

• Adipocytes may play a key role in the development of central calciphylaxis.

• Calciphylaxis remains a ‘clinical diagnosis’.
Calciphylaxis: who is at risk?

• White, female, obese, diabetic patients with worse CKD-MBD parameters at dialysis initiation

• Arguably many patients on dialysis are at risk for CUA yet few will actually develop it – in fact, the majority will not

• overall incidence of 3.49 per 1000 patient years
Why so many at risk yet so few develop?

• Triggers
  – Vitamin K antagonism
  – Skin trauma
  – Thrombotic disorders
  – Genetic predisposition

Calciphylaxis is a condition of induced systemic hypersensitivity in which, during a “critical period” after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone, sodium sulfathiazole), treatment with certain challengers (for example, metallic salts,
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</tbody>
</table>
Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry

Vincent M. Brandenburg\textsuperscript{1,2}, Rafael Kramann\textsuperscript{2,3}, Hansjörg Rothe\textsuperscript{4}, Nadine Kaesler\textsuperscript{3}, Joanna Korbiel\textsuperscript{5}, Paula Specht\textsuperscript{1}, Sophia Schmitz\textsuperscript{6}, Thilo Krüger\textsuperscript{3}, Jürgen Floege\textsuperscript{2,3} and Markus Ketteler\textsuperscript{4}

Table 3. Medication use in the group of dialysis patients at the time of CUA development\textsuperscript{a}

<table>
<thead>
<tr>
<th>Medication\textsuperscript{a}</th>
<th>All HD/HDF, patients, $n = 193$</th>
<th>PD, $n = 25$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Active vitamin D (calcitriol, paricalcitol, others)</td>
<td>102 (53%)</td>
<td>87 (45%)</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>50 (26%)</td>
<td>137 (71%)</td>
</tr>
<tr>
<td>Any phosphate binder (PB)\textsuperscript{b}</td>
<td>149 (77%)</td>
<td>41 (21%)</td>
</tr>
<tr>
<td>Calcium-containing PB\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevelamer\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanthanum carbonate\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other PB\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKAs</td>
<td>98 (51%)</td>
<td>93 (48%)</td>
</tr>
<tr>
<td>Erythropoietin and other</td>
<td>160 (83%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents, ESAs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of micro-vessel Calcification

Phosphate uptake by PiT-1 and PiT-2

VSMCs

- Osteoblastic
- Transdifferentiation

Nidus Formation

Promoters of Vascular Calcification

Inhibitors of Vascular Calcification

- Matrix Gla Protein
- Fetuin-A
- Magnesium
Vitamin K cycle

- **Diet**

  - Vitamin K-dependent carboxylation
    - Via BMP-2 inhibition
    - Arteriolar calcification in CUA

  - Uncarboxylated MGP (inactive)
  - Carboxylated MGP (active)

  - Vitamin K epoxide reductase
  - Vitamin K-epoxide reductase
  - Vitamin K hydroquinone
  - Quinone reductase

- **Protein**
  - γ-glutamyl carboxylase
  - γ-carboxylated protein

- **1000s**
**Dietary vitamin K and therapeutic warfarin alter the susceptibility to vascular calcification in experimental chronic kidney disease**

Kristin M. McCabe¹, Sarah L. Booth², Xueyan Fu², Navid Shobeiri¹, Judith J. Pang¹, Michael A. Adams¹ and Rachel M. Holden³

---

**Male Sprague Dawley rats**
Age: 14 weeks (N=69)

- 0.25% dietary adenine (n=39)
- No dietary adenine (n=30)

6 rats for baseline measurements

- Stratified by serum creatinine

- High vitamin K (100 mg/kg food, n=8)
- Low vitamin K (0.1-0.2 mg/kg food, n=16)
- Warfarin (0.1 mg/kgBW/day, n=9)

- High vitamin K (100 mg/kg food, n=6)
- Low vitamin K (0.1-0.2 mg/kg food, n=12)
- Warfarin (0.1 mg/kgBW/day, n=6)

3 weeks → 4 weeks
Warfarin lowered tissue vitamin K levels but did not cause VC in healthy rats.
Triggers: Vitamin K

Calciphylaxis characterized by relative reductions in carboxylated MGP and elevated uncarboxylated MGP in biopsy samples
Calciphylaxis patients have low VK status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=20)</th>
<th>Controls (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58 ± 16</td>
<td>62 ± 14</td>
<td>NA</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>35</td>
<td>35</td>
<td>NA</td>
</tr>
<tr>
<td>Non-White race, %</td>
<td>10</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>Warfarin therapy, %</td>
<td>30</td>
<td>30</td>
<td>NA</td>
</tr>
</tbody>
</table>

Prevalence of vitamin K deficiency, %

Adipocytes secrete MGP

Using gene expression to predict the secretome of differentiating human preadipocytes

DM Mutch¹,²,³,⁵, C Rouault¹,²,³, M Keophiphath¹,²,³, D Lacasa¹,²,³ and K Clément¹,²,³,⁴

MGP protein detected in the secretion media of adipocytes

Triggers: Trauma

Figure 2. ORs of future CUA involving lower abdomen and/or upper thigh areas by number of insulin injections per day at hemodialysis initiation. Model 1 is an unadjusted model; model 2 is adjusted for age, race, and sex; model 3 is adjusted for covariates.

Triggers: Thrombophilia

JAMA Dermatology | Original Investigation

Association Between Hypercoagulable Conditions and Calciphylaxis in Patients With Renal Disease
A Case-Control Study

<table>
<thead>
<tr>
<th>Laboratory Panel and Hypercoagulable Definition</th>
<th>Cases (n = 28)</th>
<th>Controls (n = 43)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III, functional/antigen &lt;80%</td>
<td>16 (5, 31)</td>
<td>7 (1, 14)</td>
<td>.63</td>
</tr>
<tr>
<td>Anticardiolipin antibodies, IgG/IgM &gt;15 U</td>
<td>21 (4, 19)</td>
<td>9 (2, 22)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Factor V Leiden, heterozygous mutation</td>
<td>18 (0)</td>
<td>6 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Factor VIII, &gt;200%</td>
<td>4 (4, 100)</td>
<td>2 (0)</td>
<td>.07</td>
</tr>
<tr>
<td>Heparin PF4 antibody, IgG HIT antibodies detected</td>
<td>14 (2, 14)</td>
<td>9 (2, 22)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Homocysteine level, &gt;1.62 mg/L</td>
<td>15 (12, 80)</td>
<td>9 (6, 67)</td>
<td>.64</td>
</tr>
<tr>
<td>Lupus anticoagulant, screening and confirmatory positive test result</td>
<td>23 (12, 52)</td>
<td>9 (0)</td>
<td>.01</td>
</tr>
<tr>
<td>Protein C, functional/antigen &lt;70% or activity &lt;55%</td>
<td>16 (8, 50)</td>
<td>4 (0)</td>
<td>.12</td>
</tr>
<tr>
<td>Protein S, functional/antigen &lt;70% or activity &lt;55%</td>
<td>16 (6, 40)</td>
<td>5 (3, 60)</td>
<td>.61</td>
</tr>
<tr>
<td>Prothrombin, G20210A mutation</td>
<td>10 (0)</td>
<td>2 (0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Any thrombophilia, ≥1 abnormal test result</td>
<td>27 (21, 78)</td>
<td>20 (12, 60)</td>
<td>.21</td>
</tr>
<tr>
<td>Combined thrombophilia, ≥2 abnormal test results</td>
<td>24 (15, 63)</td>
<td>12 (1, 8)</td>
<td>.004</td>
</tr>
</tbody>
</table>
Triggers: Genetic predisposition

Ecto-5'-Nucleotidase CD73 (NT5E), vitamin D receptor and FGF23 gene polymorphisms may play a role in the development of calcific uremic arteriolopathy in dialysis patients – Data from the German Calciphylaxis Registry

Hansjörg Rothe¹,² *, Vincent Brandenburg³, Margot Haun⁴, Barbara Kollerits⁴, Florian Kronenberg⁴, Markus Ketteler¹, Christoph Wanner²

• 144 HD patients from the German calciphylaxis registry were compared with 370 dialysis patients without calciphylaxis
• Investigation of 10 target genes
Triggers: genetic predisposition

<table>
<thead>
<tr>
<th>Gene encoding</th>
<th>SNP</th>
<th>OR^{S}</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD73</td>
<td>Rs9444348</td>
<td>1.48</td>
<td>1.11–1.97</td>
<td>0.008</td>
</tr>
<tr>
<td>FGF23</td>
<td>Rs12812339</td>
<td>0.58</td>
<td>0.38–0.87</td>
<td>0.009</td>
</tr>
<tr>
<td>FGF23</td>
<td>Rs7310492</td>
<td>1.49</td>
<td>1.06–2.09</td>
<td>0.021</td>
</tr>
<tr>
<td>CD73</td>
<td>Rs4431401</td>
<td>1.71</td>
<td>1.08–2.71</td>
<td>0.023</td>
</tr>
<tr>
<td>VDR</td>
<td>Rs10783223</td>
<td>0.73</td>
<td>0.55–0.96</td>
<td>0.025</td>
</tr>
<tr>
<td>VDR</td>
<td>Rs17882106</td>
<td>1.65</td>
<td>1.06–2.56</td>
<td>0.026</td>
</tr>
<tr>
<td>FGF23</td>
<td>Rs6489536</td>
<td>0.70</td>
<td>0.51–0.96</td>
<td>0.026</td>
</tr>
<tr>
<td>FGF23</td>
<td>Rs11063118</td>
<td>1.41</td>
<td>1.03–1.92</td>
<td>0.032</td>
</tr>
<tr>
<td>FGF23</td>
<td>Rs13312747</td>
<td>1.50</td>
<td>1.01–2.25</td>
<td>0.047</td>
</tr>
</tbody>
</table>
Calciphylaxis – other potential triggers

- Autoimmune disorders
- Recurrent hypotension
- Vitamin D analogues
Calcitriol treatment in rats with CKD
CKD rats treated with 20 ng/kg calcitriol daily
Two cases – triggers

- Patient A – 2004
  - ESKD on PD
  - Poor phosphate control
- Obese
- Insulin injections

- Patient B - 2016
  - KT
  - Normal phosphate
- Warfarin
- Calcitriol
Management...evidence is lacking...
Nephrologist

- Clinical diagnosis
  - Skin biopsy
- Dialysis prescription
- CKD-MBD management
- Decision regarding antibiotics
- Risks/benefits of warfarin and alternative agents (if applicable)
- Specific treatment decisions
- Enroll in registry or clinical trial

Adapted from Curr Opin Nephrol Hypertens.
Skin biopsy: when to perform

• To support your clinical diagnosis and rule out other conditions
• Early, atypical lesions
• Research studies
• Calciphylaxis suspected in non-ESKD patient

• Punch biopsy safer but has limited depth and can be non-diagnostic
• Biopsy active lesion margin rather then central or necrotic area
• Special stains should include von Kossa
Skin biopsy: when not to perform

• Not needed for a patient with ESKD with classic presentation of a painful necrotic ulcer covered with a black eschar

• A skin biopsy may be contra-indicated in:
  – Acral, penile or infected lesions

• High risk of provoking new, non-healing ulcers and infection
Dialysis prescription

• Increase length or frequency
  – Warranted for patients with severe CKD-MBD parameters
  – No data

• Transition to hemodialysis for patients on PD
  – No data

• Kidney transplantation
  – Case series of 3 patients receiving urgent KT after 2 to 4 weeks of onset of calcipylaxis  *Transplantation Direct 2016*
CKD-MBD parameters + other measures

- Discontinue warfarin
- Rotate insulin injection sites
- Stop vitamin D and calcium
- Avoid high dialysate calcium
- ? Parathyroidectomy
  - Optimal PTH is not known
  - Risk of ABD long-term
Parathyroidectomy – what is the evidence?

- Single-center studies
- All retrospective
  - Selection bias
  - Confounding
- Details regarding actual surgical procedure and risks/complications are limited
- Risk of hungry bone syndrome requiring calcium and calcitriol
- Not recommended by ‘experts’ in the era of calcimimetics
  - EVOLVE trial showed a reduced incidence of calciphylaxis in the cinacalcet group
Dermatologist

- Clinical diagnosis
- Skin biopsy
- Wound care
- Decision regarding antibiotics

Pathologist

- Skin histopathology review
- Request for special stains (e.g. von Kossa)

Adapted from *Curr Opin Nephrol Hypertens* 2015, 24:53
Radiologist

- Evidence of calcification on X-ray, CT or bone scan

Adapted from Curr Opin Nephrol Hypertens
Diagnosis: Imaging studies

• May support the diagnosis when a biopsy is inconclusive or contraindicated
Increased radiotracer uptake in soft tissues on nuclear bone scanning
Pain and Palliative Care

- Pain medications
  - Opiates
  - Opiate alternatives
  - Spinal anesthetic agents

- Goals of care discussions

Adapted from *Curr Opin Nephrol Hypertens* 2015, 24
Surgeon and Wound Care Nurse

- Clinical diagnosis
- Surgical debridement
- Wound care
- Dressing changes
- Chemical wound debridement
- Hyperbaric oxygen

Adapted from *Curr Opin Nephrol Hypertens*
Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review

JENNIFER AN, BRIDGET DEVANEY, KHAI YANG OOI, SHARON FORD, GEOFF FRAWLEY and SOLOMON MENAHEM

• 46 patients
• 44 sessions over 2 months led to complete healing in half the patients with peripheral disease
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cohort</th>
<th>No. of HBOT treatments (range)</th>
<th>Other interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podymow et al.\textsuperscript{15}</td>
<td>2001</td>
<td>5</td>
<td>25–35</td>
<td>Nil</td>
<td>60% improved</td>
</tr>
<tr>
<td>Basile\textsuperscript{20}</td>
<td>2002</td>
<td>11</td>
<td>20–108</td>
<td>PTHX</td>
<td>40% healed</td>
</tr>
<tr>
<td>Dwyer et al.\textsuperscript{21}</td>
<td>2002</td>
<td>1</td>
<td>23</td>
<td>Not reported</td>
<td>89% improved</td>
</tr>
<tr>
<td>Edsell et al.\textsuperscript{22}</td>
<td>2008</td>
<td>20</td>
<td>17–83</td>
<td>PTHX</td>
<td>73% healed</td>
</tr>
<tr>
<td>Rogers et al.\textsuperscript{23}</td>
<td>2008</td>
<td>12</td>
<td>7–41</td>
<td>Not reported</td>
<td>100% healed</td>
</tr>
<tr>
<td>Arenas et al.\textsuperscript{24}</td>
<td>2008</td>
<td>2</td>
<td>20–30</td>
<td>Cinacalcet, STS, PTHX, sevelamer</td>
<td>55% improved</td>
</tr>
<tr>
<td>Alikadic et al.\textsuperscript{25}</td>
<td>2009</td>
<td>1</td>
<td>19</td>
<td>Iloprost infusion</td>
<td>30% healed</td>
</tr>
<tr>
<td>Baldwin et al.\textsuperscript{26}</td>
<td>2011</td>
<td>7</td>
<td>10–65</td>
<td>Cinacalcet, sevelamer, STS</td>
<td>92% healed</td>
</tr>
<tr>
<td>New et al.\textsuperscript{27}</td>
<td>2011</td>
<td>5</td>
<td>25–30</td>
<td>Calcitriol, cinacalcet, STS, PTHX, sevelamer</td>
<td>100% healed</td>
</tr>
<tr>
<td>Malabu et al.\textsuperscript{28}</td>
<td>2012</td>
<td>6</td>
<td>Not reported</td>
<td>Cinacalcet, STS, PTHX</td>
<td>86% healed</td>
</tr>
<tr>
<td>Savoia et al.\textsuperscript{29}</td>
<td>2013</td>
<td>4</td>
<td>Not reported</td>
<td>Cinacalcet, STS</td>
<td>80% healed</td>
</tr>
</tbody>
</table>
Dietitian

- Dietary phosphate restriction
- Avoiding and treating protein malnutrition

Adapted from *Curr Opin Nephrol Hypertens*
Specific pharmacotherapeutic agents

- Sodium thiosulfate
- Cinacalcet
- Vitamin K
- Bisphosphonates
Sodium Thiosulfate

- Mechanism of action – Unknown
- Hypotheses
  - Vaso-dilatory and antioxidant properties
  - Increase in calcium solubility
  - Combination with calcium to form a dialyzable salt
- Administration
  - Typical dose is 25 g IV 3x weekly during last 30-60 mins of HD
  - Dose for PD, CKD, KT, pediatrics unknown

Sodium Thiosulfate

• Limitations
  – Limited access
  – Cost $10,000

• Adverse Effects
  – Nausea, vomiting and headache
    • *Usually improve with subsequent infusions*
  – Severe metabolic acidosis
    • Unknown mechanism
    • Dose-response effect on AG
    • ? Due to oxidation of STS by the liver

---

**Box 3 | Adverse effects of STS**

- Frequently reported:
  - Nausea and vomiting
  - Headache
  - Decreased serum bicarbonate level
  - Increased serum anion gap
  - Increased serum sodium levels

- Single reports:
  - Rhinorrhea
  - Sinus congestion
  - Neurological effects (bad taste, periorbital tingling, decreased hearing)
  - Hypocalcemia with increased QT interval
  - Hunger
  - Weakness

Abbreviation: STS, sodium thiosulphate.

---

Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy

Sagar U. Nigwekar,∗† Steven M. Brunelli,‡§ Debra Meade,¶ Weiling Wang,¶ Jeffrey Hymes,¶ and Eduardo Lacson Jr.§

• Retrospective cohort study of 172 patients with calciphylaxis who were treated with STS
• No control subjects
• Incomplete follow-up for patient-level outcomes (n=53)
• Median dose was 25 g and median number of doses was 38
Among surveyed patients, calciphylaxis status was:

- resolved in 26.4%
- markedly improved in 18.9%
- improved in 28.3%
- did not improve in 5.7%
- unknown 20.8%
Table 2. Additional treatment modalities that were undertaken before or during sodium thiosulfate therapy

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation/increased dose of non-calcium-based phosphorous binder</td>
<td>59</td>
</tr>
<tr>
<td>Initiation of cinacalcet</td>
<td>57</td>
</tr>
<tr>
<td>Wound care</td>
<td>34</td>
</tr>
<tr>
<td>Discontinuation of vitamin D compounds</td>
<td>30</td>
</tr>
<tr>
<td>Increased frequency of hemodialysis sessions</td>
<td>15</td>
</tr>
<tr>
<td>Surgical parathyroidectomy</td>
<td>15</td>
</tr>
<tr>
<td>Lowering of dialysate calcium</td>
<td>15</td>
</tr>
<tr>
<td>Initiation of corticosteroids</td>
<td>9</td>
</tr>
<tr>
<td>Switching from nonselective vitamin D analogue to selective analogue</td>
<td>8</td>
</tr>
<tr>
<td>Discontinuation of warfarin</td>
<td>6</td>
</tr>
<tr>
<td>Discontinuation of calcium-based phosphate binders</td>
<td>4</td>
</tr>
</tbody>
</table>
27 HD patients treated with STS for 3 months
  – Complete remission: 52%
  – Partial remission: 19%
  – No response: 30%

High frequency of co-interventions
  • Vitamin K, HBO, PTH lowering strategies, warfarin cessation, calcium cessation, increased dialysis intensity
Vitamin K

• Some evidence from general population that vitamin K decreases calcification

<table>
<thead>
<tr>
<th></th>
<th>VitaVasK</th>
<th>iPACK-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Europe</td>
<td>Canada</td>
</tr>
<tr>
<td>Patient population</td>
<td>HD patients</td>
<td>HD patients</td>
</tr>
<tr>
<td>CAC score criteria</td>
<td>≥ 100 AUs</td>
<td>≥ 30 AUs</td>
</tr>
<tr>
<td>Outcome</td>
<td>CAC progression</td>
<td>CAC progression</td>
</tr>
<tr>
<td>Drug</td>
<td>K1</td>
<td>K1</td>
</tr>
<tr>
<td>Dose</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Frequency</td>
<td>3 times per week</td>
<td>3 times per week</td>
</tr>
<tr>
<td>Duration</td>
<td>18 months</td>
<td>12 months</td>
</tr>
</tbody>
</table>
The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial

Jürgen Floege,* Yumi Kubo,† Anna Floege,* Glenn M. Chertow,‡ and Patrick S. Parfrey§

• 3,883 HD patients with sHPT
• Randomly assigned 1:1 to receive
  – Cinacalcet (Sensipar or Mimpara, Amgen, Inc.); or
  – Placebo
• + Conventional CKD-mineral & bone disorder therapies
• F/U 64 months
  – 6 (cinacalcet) and 18 patients (placebo) developed CUA
### Table 5. Multivariate regression using Fine-Gray subdistributional hazards model of calcific uremic arteriolopathy adverse events (safety analysis set)

<table>
<thead>
<tr>
<th>Multivariate Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (cinacalcet versus placebo)</td>
<td>0.25 (0.10 to 0.67)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex (reference, female)</td>
<td>0.33 (0.14 to 0.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (per kg/m²)</td>
<td>1.09 (1.05 to 1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (per 10 mmHg)</td>
<td>1.50 (1.19 to 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of dyslipidemia</td>
<td>2.15 (0.90 to 5.15)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of parathyroidectomy</td>
<td>5.79 (1.79 to 18.70)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline tobacco use (reference, never use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1.79 (0.54 to 5.89)</td>
<td>0.34</td>
</tr>
<tr>
<td>Former</td>
<td>3.04 (1.19 to 7.74)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Baseline variables were included using backward elimination. Heart failure and diabetes mellitus were removed during the backward elimination procedure at a significance level of 0.10. Additional baseline variables of age, vitamin K antagonist use, vitamin D sterol use, and peripheral vascular disease were evaluated but not included in the multivariate regression model using the backward elimination procedure because they did not meet the entry criteria, $P<0.25$ in a univariate model. 95% CI, 95% confidence interval.
ADVANCE: The first RCT to show that Cinacalcet may attenuate the progression of valvular calcification in SHPT
Bisphosphonates

• Pyrophosphate analogues
• Inhibition of osteoclasts
• Prospective series only
Patient A – central calciphylaxis

- 42 year old female
- Obese
- ESKD secondary to FSGS
- Type 2 DM on insulin injections
- Peritoneal dialysis
- Presented April, 2004
Patient A - 2004

- Calcium discontinued; NCPB started
- Switched to daily HD
- Surgical debridement and wound care
- Hyperbaric oxygen – 25 sessions
Patient B – 2016

- 55 year old male
- Normal weight
- ESKD secondary to hypertension
- Kidney transplant 1991
- Baseline creatinine ~ 180 umol/L
- Presented May, 2016
Patient B - 2016

- Warfarin discontinued
- Calcitriol discontinued
- Cinacalcet started
- Surgical debridement and wound care
- Vitamin K 10 mg PO thrice weekly x 6 weeks
- Bisphosphonate – 30 mg IV x 1 dose
- Hyperbaric oxygen – 23 sessions
Where are we in 2018?

- we have a rare disease with a rising incidence
- we have therapies that we try
- we have no rigorous scientific evidence

Incidence per 10,000 dialysis patients

Nigwekar et al. JGIM. 2014;29 (3):724-731
What is the answer?

Clinical observations
• VK antagonism

Translational Medicine
What is the answer?

Translational Medicine
What is the answer?

Translational Medicine

High K diet
What is the answer?

Translational Medicine

VitK-CUA trial
Improving the evidence: RCT of Vitamin K

<table>
<thead>
<tr>
<th>Study eligibility: adult HD patients with calciphylaxis</th>
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<tbody>
<tr>
<td>Study intervention: vitamin K1 10 mg three times/week for 12 weeks</td>
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<td>Outcomes: pain, skin lesions</td>
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</table>

| VitK-CUA | Clinicaltrials.gov number, NCT02278692 | Phase 2, clinical trial | Massachusetts General Hospital | Single-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the biological efficacy and safety of phytonadione (vitamin K1) in hemodialysis patients with calciphylaxis |

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What is the answer?

Clinical observations
- CKD-MBD parameters
- CKD-MBD treatments
- Obesity
- Trauma

Translational Medicine
What is the answer?

Osteogenic program
‘Adipocyte calcification’

Translational Medicine
What is the answer?

Translational Medicine
## Improving the evidence: Active registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Type</th>
<th>Institution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuCalNet Registry</td>
<td>Prospective registry</td>
<td>RWTH Aachen University</td>
<td>Observational, prospective, non-interventional collection of data and samples from patients with uremic and non-uremic calciphylaxis</td>
</tr>
<tr>
<td>Partners Calciphylaxis Biobank</td>
<td>Prospective registry</td>
<td>Massachusetts General Hospital</td>
<td>Observational, prospective, non-interventional collection of data and samples from patients with uremic and non-uremic calciphylaxis</td>
</tr>
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<td>The UK Calciphylaxis Study</td>
<td>Prospective registry</td>
<td>Salford Royal NHS Foundation Trust (UK)</td>
<td>Observational, prospective, non-interventional collection of data and samples from patients with calciphylaxis in the setting of chronic kidney disease</td>
</tr>
</tbody>
</table>
Improving the evidence: Two RCTs of sodium thiosulfate

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study ID</th>
<th>Study Type</th>
<th>Sponsor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A clinical trial with Sodium Thiosulfate for the treatment of Calciphylaxis</td>
<td>ISRCTN number, ISRCTN73380053</td>
<td>Phase 2/3, clinical trial</td>
<td>Dr. F. Köhler Chemie GmbH (Germany)</td>
<td>Multicenter, open-label clinical trial to evaluate the efficacy of intravenous Sodium Thiosulfate for treatment of calciphylaxis wounds in hemodialysis patients</td>
</tr>
<tr>
<td>CALISTA Trial</td>
<td>Clinicaltrials.gov number, NCT03150420</td>
<td>Phase 3, clinical trial</td>
<td>Hope Pharmaceuticals</td>
<td>Multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of intravenous Sodium Thiosulfate Injection for treatment of acute calciphylaxis-associated pain in hemodialysis patients</td>
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</table>
The way forward
Thank you