Calciphylaxis: Incidence and Management in PD patients

Sagar Nigwekar MD, MMScc
Massachusetts General Hospital
Harvard Medical School
E-mail: snigwekar@mgh.harvard.edu

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Objectives

1. To review calciphylaxis epidemiology in patients with end stage renal disease

2. To review risk factors for calciphylaxis in peritoneal dialysis patients

3. To outline management approach to calciphylaxis in patients on PD
Calciphylaxis is a disorder of calcification and thrombosis of dermal arterioles leading to painful skin lesions.

Morphology of calciphylaxis skin lesions

One-year mortality in calciphylaxis patients

Nigwekar et al. AJKD. 2015 Jul;66(1):133-46
Histopathological features of calciphylaxis

- Calcification and subintimal fibroplasia of arteriole
- Thrombotic occlusion of arteriole
- Cutaneous ischemic necrosis
Calciphylaxis patients have diffuse vascular calcifications

**Graph:**

- **X-axis:** Aorta, Coronaries, Visceral, Pelvis, Mammography
- **Y-axis:** 0 to 10
- **Legend:**
  - Cases
  - Controls

*Courtesy Drs. Novak and Harisinghani*
Rats in experimental calciphylaxis developed extensive soft tissue calcifications but did not develop small artery or arteriolar calcifications that are characteristic of human calciphylaxis. Also, unlike human calciphylaxis, these rats were able to cast off the “cutaneous molt” and replace it with new dermis without any features of calciphylaxis.
Early reports of human calciphylaxis

Eisenberg et al. NEJM. 1963
Gipstein et al. Archives of Internal Med. 1976
Calciphylaxis case frequency at the Partners hospitals (HD)

Calciphylaxis identification using a surrogate strategy

ICD-9 code 275.49
Chondrocalcinosis
Nephrocalcinosis
Vascular calcification
Oxalate related arthritis
Apatite related arthropathy
Calciphylaxis following trauma
Intervertebral disc calcification
Bartter’s syndrome with hypercalciuria

Skin biopsy
CPT codes 110xx ICD-9 code 86.1
Excision biopsy
Calciphylaxis incidence per 10,000 maintenance HD patients in the USRDS

Nigwekar et al. JGIM. 2014;29 (3):724-731
Risk factor associations for calciphylaxis

• **Demographics and co-morbidities**
  – Caucasian race
  – Female gender
  – Obesity
  – Autoimmune disease
  – Hypercoagulable state

• **Mineral bone disease**
  – Hypercalcemia
  – Hyperphosphatemia
  – Severe hyperparathyroidism

• **Hypoalalbuminemia**

• **Medications**
  – Calcium-based binders
  – Vitamin D
  – Warfarin
  – Iron therapy
  – Corticosteroid therapy

• **Dialysis vintage**

The Tipping Point
How Little Things Can Make a Big Difference

Malcolm Gladwell

“A fascinating book that makes you see the world in a different way.” — Fortune
<table>
<thead>
<tr>
<th>Condition</th>
<th>Features of clinical mimic</th>
<th>Features of calciphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic vascular disease</td>
<td>Symptoms of claudication, weak peripheral pulses, distal distribution, abnormal ankle-brachial index</td>
<td>Can be proximal or distal distribution, severe pain, dermal arteriolar calcification on skin biopsy</td>
</tr>
<tr>
<td>Cholesterol embolization</td>
<td>Usually in acral distribution, may have features associated with renal or gastrointestinal ischemia, cholesterol clefts on skin biopsy</td>
<td>Can be proximal or distal distribution, dermal arteriolar calcification on skin biopsy</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>Brawny plaques, thickened skin, history of exposure to gadolinium, moderate intensity pain, marked increase in spindle cells and fibrosis on skin biopsy</td>
<td>Severe pain, dermal arteriolar calcification on skin biopsy</td>
</tr>
<tr>
<td>Oxalate vasculopathy</td>
<td>Acral distribution, history of calcium oxalate stones, birefringent, yellowish-brown, polarizable crystalline material deposition in the dermis and arteriolar wall on skin biopsy</td>
<td>Can be proximal or distal distribution, calcium deposits non-polarizable</td>
</tr>
<tr>
<td>Purpura fulminans</td>
<td>Usually seen in the settings such as septic shock or disseminated intravascular coagulation, diffuse body distribution, rapid progression, clinical features of shock</td>
<td>Unlikely to have diffuse whole body distribution, absence of serological features of disseminated intravascular coagulation, dermal arteriolar calcification on skin biopsy</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Systemic features of vasculitis, serological test abnormalities (e.g. cryoglobulins), no dermal arteriolar calcification on skin biopsy, unlikely to have full-thickness necrosis or large areas of involvement</td>
<td>Absence of systemic features and serological abnormalities of vasculitis (unless autoimmune disease is a trigger for calciphylaxis), black eschar, dermal arteriolar calcification on skin biopsy</td>
</tr>
<tr>
<td>Warfarin necrosis</td>
<td>Typically seen within the first 10 days of warfarin initiation, manifestation of paradoxical hypercoagulable state created by a transient imbalance in the procoagulant and anticoagulant pathways warfarin discontinuation associated with clinical improvement in majority of cases</td>
<td>Warfarin exposure of prolonged duration when calciphylaxis associated with warfarin therapy, black eschar, dermal arteriolar calcification on skin biopsy</td>
</tr>
</tbody>
</table>
Calciphylaxis in PD patients

• What is the Incidence?
  – Limited data
  – 0.97% annual incidence

• Does PD increase calciphylaxis risk?
  – One prospective study reported increased risk but findings have not been confirmed
  – ? Related to calcium binders and higher calcium bath

MGH calciphylaxis study

• N=69 (CAPD=7, HD= 62)

• Calciphylaxis cases identified retrospectively using natural language processing and pathology records review

• Prospective enrollment ongoing

Nigwekar et al. ASN 2013
Comparison of calciphylaxis cases (HD) with controls (HD)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cases (n=62)</th>
<th>Controls (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58 ± 14</td>
<td>58 ± 13</td>
<td>0.94</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>68</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>White race (%)</td>
<td>64</td>
<td>59</td>
<td>0.62</td>
</tr>
</tbody>
</table>
## Comparison of calciphylaxis cases (HD) with controls (HD)

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Cases (n=62)</th>
<th>Controls (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis vintage (yr)</td>
<td>4.7 [2.6-5.8]</td>
<td>4.9 [2.7-6.2]</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>44</td>
<td>42</td>
<td>0.88</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>37</td>
<td>35</td>
<td>0.75</td>
</tr>
<tr>
<td>Autoimmune disease (%)</td>
<td>9</td>
<td>8</td>
<td>0.82</td>
</tr>
<tr>
<td>Macrovascular disease (%)</td>
<td>45</td>
<td>44</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Comparison of calciphylaxis cases (HD) with controls (HD)

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Cases (n=62)</th>
<th>Controls (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected calcium (mg/dL)</td>
<td>8.9 [8.4-9.4]</td>
<td>8.8 [8.1-9.1]</td>
<td>0.03</td>
</tr>
<tr>
<td>Phosphorous (mg/dL)</td>
<td>5.7 [5.2-5.9]</td>
<td>5.4 [4.6-5.7]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcium-phosphorous product</td>
<td>49.7 [43.5-55.6]</td>
<td>45.4 [40.3-49.2]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>123 [84-186]</td>
<td>120 [67-165]</td>
<td>0.11</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)</td>
<td>297 [129-453]</td>
<td>285 [136-421]</td>
<td>0.60</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.9 [2.5-3.4]</td>
<td>3.6 [3.1-3.9]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>98 [67-110]</td>
<td>103 [64-118]</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Comparison of calciphylaxis cases (HD) with controls (HD)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Cases (n=62)</th>
<th>Controls (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (%)</td>
<td>44</td>
<td>19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcitriol (%)</td>
<td>15</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Selective vitamin D analogues (%)</td>
<td>47</td>
<td>48</td>
<td>0.92</td>
</tr>
<tr>
<td>Calcium-based phosphate binders (%)</td>
<td>32</td>
<td>33</td>
<td>0.91</td>
</tr>
<tr>
<td>Cinacalcet (%)</td>
<td>18</td>
<td>22</td>
<td>0.67</td>
</tr>
<tr>
<td>Iron therapy (%)</td>
<td>19</td>
<td>23</td>
<td>0.61</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>19</td>
<td>39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACE inhibitor/ARB (%)</td>
<td>25</td>
<td>27</td>
<td>0.52</td>
</tr>
</tbody>
</table>

MGH calciphylaxis study: PD vs. HD

• PD calciphylaxis patients:
  – younger than HD calciphylaxis patients (median age 50 vs. 62 years, p=0.03)
  – more likely to be non-Caucasian (62% vs. 36%, p=0.04)

• Median dialysis vintage was 5.1 years for PD calciphylaxis patients and 4.8 years for HD calciphylaxis patients (p=0.10)

Nigwekar et al. ASN 2013
MGH calciphylaxis study: PD vs. HD

- Diabetes mellitus: HD 28%, PD 35%, P=0.10
- Macrovascular disease: HD 31%, PD 34%, P=0.10
- Obesity: HD 37%, PD 57%, P=0.01
- Hypoalbuminemia: HD 65%, PD 100%, P=0.02
- Warfarin: HD 44%, PD 71%, P=0.01
- Calcium based phosphate binders: HD 33%, PD 29%, P=0.11
- Vitamin D therapy: HD 49%, PD 45%, P=0.13

Nigwekar et al. ASN 2013
## MGH calciphylaxis study: PD vs. HD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD calciphylaxis cases (n=7)</th>
<th>HD calciphylaxis cases (n=62)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium, corrected (mg/dL)</td>
<td>9.0 [8.5-9.5]</td>
<td>8.9 [8.4-9.4]</td>
<td>0.59</td>
</tr>
<tr>
<td>Serum phosphorous (mg/dL)</td>
<td>5.4 [5.3-6.0]</td>
<td>5.7 [5.2-5.9]</td>
<td>0.33</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (U/L)</td>
<td>131 [81-191]</td>
<td>123 [84-186]</td>
<td>0.21</td>
</tr>
<tr>
<td>Serum parathyroid hormone (pg/mL)</td>
<td>291 [141-423]</td>
<td>297 [129-453]</td>
<td>0.38</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (ng/mL)</td>
<td>20 [10-25]</td>
<td>16 [11-24]</td>
<td>0.20</td>
</tr>
</tbody>
</table>
MGH calciphylaxis study: PD vs. HD

• Higher prevalence of calciphylaxis risk factors (such as warfarin and hypoalbuminemia) rather than dialysis modality likely explains calciphylaxis development in PD patients.

• Prospective studies are needed to confirm these findings.

• More judicious warfarin use and attention to malnutrition-inflammation complex may prevent calciphylaxis in PD patients.
Potential biological link between warfarin and calciphylaxis

-84 amino acid protein
-requires vitamin K dependent carboxylation for its activation
-vascular calcification inhibitor
-proposed to inhibit BMP signaling; inhibits release of membrane bound vesicles and also has been shown to prevent progression of calcification by direct binding to calcium phosphate
-produced in vascular smooth muscle cells and chondrocytes

Dermal arteriolar calcification

Nigwekar et al. ASN 2015
Oxidative stress, inflammation and vascular calcification play a major role in calciphylaxis.
How to prevent calciphylaxis in PD patients?

- Identification of “At Risk” patients and early lesions
- Risk-benefit assessment for warfarin
- Optimizing nutrition status
- Management of chronic inflammation
- Mineral bone disease management
  - Non-calcium based binders
  - Selective vitamin D analogues
  - Low calcium bath
  - Cinacalcet
  - Surgical parathyroidectomy
  - Avoiding oversuppression of PTH

Rigorous scientific evidence is limited
How to treat calciphylaxis in PD patients?

Rigorous scientific evidence is limited

– Multi-disciplinary management
– Wound management
– Pain and palliative care
– Warfarin discontinuation
– Management of chronic inflammation
– Optimizing nutrition status
Multi-disciplinary and collaborative approach

- Nephrology team
  - Dialysis prescription
  - Sodium thiosulfate treatment
  - MBD management
  - Warfarin risk/benefit

- Dermatology
  - Skin biopsy
  - Intra-lesional sodium thiosulfate

- Pathology

- Wound care

- Plastic/Burn surgery
  - Debridement
  - Hyperbaric oxygen

- Pain/Palliative care

- Radiology
  - Tc nuclear scan

- Hematology
  - Anticoagulation
  - Hyper-coagulability work-up
How to treat calciphylaxis in PD patients?

- Optimizing dialysis adequacy
- Transition to HD
  - Literature inconsistent
  - Logistical issues to be taken into consideration
- Sodium thiosulfate
  - Evidence for safety and efficacy
  - Route of administration

*Rigorous scientific evidence is limited*

*FINE et al. Perit Dial Int. 2008 May-Jun;28(3):268-70*
Sodium thiosulfate has anti-oxidant and anti-calcification properties; however its efficacy in calciphylaxis is unclear.
Intravenous sodium thiosulfate and calciphylaxis lesions (HD)

Overall mortality during the study follow-up was 42% and one-year mortality was 35%

Sodium thiosulfate adverse events (HD)

- Nausea and vomiting: 19% (self-limited in all but one)

- Bad taste with periorbital tingling, fatigue, hypotension and decreased hearing were reported but were rare (each < 2 %) and self-limited

- None of the deaths during the study period were attributed to sodium thiosulfate
Treatments frequently administered along with sodium thiosulfate (N=451)

- Increased phosphate binder dose: 61.2%
- Wound care/debridement: 52.9%
- Sevelamer initiation: 45.5%
- Vitamin D discontinuation: 41.5%
- Calcium compounds discontinuation: 34.1%
- Cinacalcet initiation: 32.1%
- Lowering of calcium bath: 29.2%
- Increased dialysis duration or frequency: 28.7%
- Surgical Parathyroidectomy: 12.4%
- Warfarin discontinuation: 12.3%
- Lanthanum carbonate initiation: 10.6%
- Calcium acetate initiation: 10.4%
- Corticosteroid treatment: 5.1%

Nigwekar et al. ASN 2014
Intra-lesional sodium thiosulfate in calciphylaxis

Strazulla, Nigwekar, et al. JAMA Derm June 2013
Intra-lesional sodium thiosulfate in calciphylaxis
Role of bisphosphonates in calciphylaxis: postulated mechanisms

- Pyrophosphate analogues
- Inhibition of osteoclasts into mature cells
- Anti-inflammatory properties
  - Reduced macrophage activity and cytokines secretion

Conclusions

• Calciphylaxis is a rare but devastating disease in PD patients.
• Recent data support warfarin, hypoalbuminemia and mineral abnormalities as calciphylaxis risk factors.
• Prevention, early detection, and multi-disciplinary management are critical.
• More data are needed to address the efficacy of sodium thiosulfate and transition to HD in PD patients.
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- MGH CAPD unit
- USRDS
  - Craig Solid, PhD
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- FMCNA
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Contact Information:
Sagar Nigwekar MD, MMSc
Massachusetts General Hospital
55 Fruit Street, GRB 1008
Boston, MA 02114
E-mail: snigwekar@mgh.harvard.edu
Extra slides
Vitamin K-CUA
Pilot double-blind randomized controlled trial
NCT02278692

Study eligibility: adult patients with calciphylaxis

Study intervention: Oral vitamin K 10 mg three times a week for 12 weeks

Study protocol: blood samples drawn at baseline and at the end of study, clinical follow-up every 4 weeks during study period

Contact:
Sagar Nigwekar, MD, MMSc
165 Cambridge Street, Suite 302,
Boston, MA 02114
Phone: 617 726 7872
Email: snigwekar@mgh.harvard.edu
Radiological evaluation of calciphylaxis lacks specificity
Calciphylaxis most commonly occurs in ESRD patients; however it has also been described in patients with normal renal function.

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Hyperparathyroidism</td>
<td>27.8</td>
</tr>
<tr>
<td>Malignancy</td>
<td>22.8</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>16.7</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>11.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*Nigwekar et al. CJASN. 2008 Jul;3(4):1139-43*
### Role of parathyroidectomy in calciphylaxis

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study design and patients</th>
<th>Parathyroidectomy surgery details</th>
<th>Results</th>
</tr>
</thead>
</table>
| Duffy et al, 2006⁸   | Single center, retrospective<br> N=15; 6 were treated with surgical parathyroidectomy and 9 were not<br> Patients who underwent surgical parathyroidectomy were younger (48 vs. 56 years) and had higher PTH levels (557 ± 278 vs. 225 ± 111 pg/ml) compared to those who did not | Of the 6 patients who underwent parathyroidectomies, 4 underwent subtotal and 2 underwent total parathyroidectomies; postoperative PTH 22 ± 5.5 pg/ml | Wound healing: 100% in parathyroidectomy patients vs. 22 % in non-parathyroidectomy group (p=0.006)  
Median survival 39 months in parathyroidectomy patients vs. 3 months in non-parathyroidectomy patients (p=0.017) |
| Weenig et al, 2006⁹ | Single center, retrospective<br> N=49; 16 were treated with surgical parathyroidectomy and 33 were not<br> Comparison of characteristics patients who underwent surgical parathyroidectomy vs. those who did not was not provided | Not provided | One year survival rate: 33.3% for parathyroidectomy patients vs. 38.3% for non-parathyroidectomy patients (p=0.92) |
| Lal et al, 2009¹⁰    | Single center, retrospective<br> N=26; 9 were treated with surgical parathyroidectomy and 17 were not<br> Patients who underwent surgical parathyroidectomy had higher PTH levels (663 ± 87 vs. 84 ± 76 pg/ml) compared to those who did not | Of the 9 patients who underwent parathyroidectomies, 5 underwent subtotal, 2 underwent total parathyroidectomies and details were unknown in 2 patients; postoperative PTH levels not available | Median survival 15 months in parathyroidectomy patients vs. 5 months in non-parathyroidectomy patients (p=0.22)  
Patients who underwent parathyroidectomy and surgical wound debridement had a trend towards improved survival compared to those patients who did not undergo these procedures (p=0.09) |