Calciphylaxis

From basic mechanisms to clinical management

Dr. Rachel M. Holden

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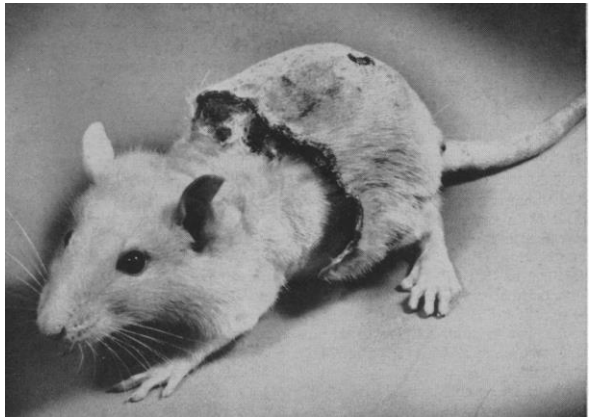
BC KIDNEY DAYS

Cutaneous Molt Induced by Calciphylaxis in the Rat

Author(s): Hans Selye, G. Gentile and P. Prioreschi

Source: *Science*, New Series, Vol. 134, No. 3493 (Dec. 8, 1961), pp. 1876-1877

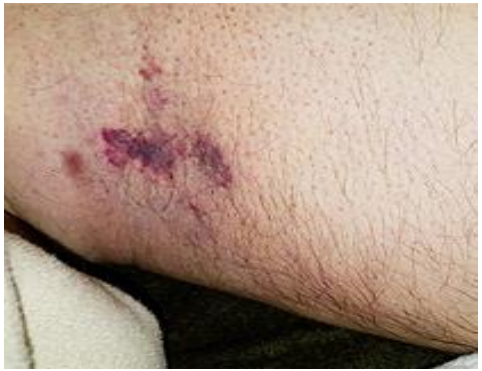


Calciphylaxis is a condition of induced systemic hypersensitivity in which, during a "critical period" after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone, sodium sulfathiazole), treatment with certain challengers (for example, metallic salts, albumen)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

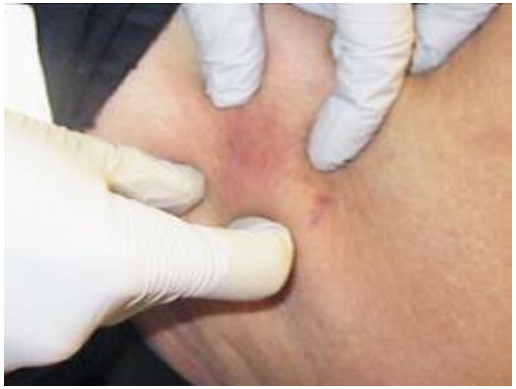
Calciphylaxis - definition

- Rare, life-threatening disorder characterized by:

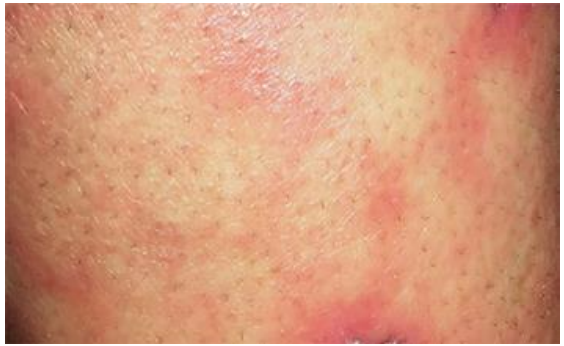
  Occlusion of micro vessels in the subcutaneous adipose tissue and dermis leading to intensely painful, ischemic skin lesions



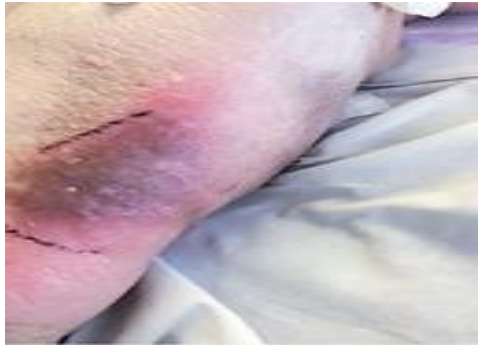
Violaceous patch



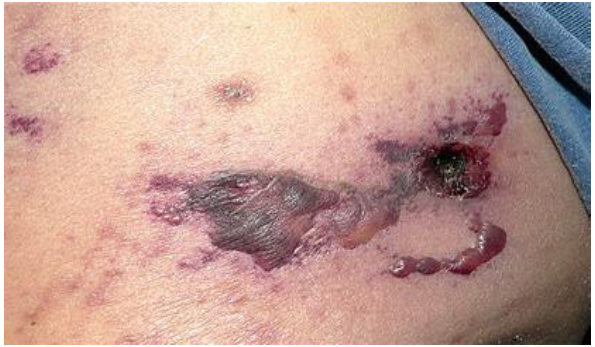
Sub-cutaneous nodule



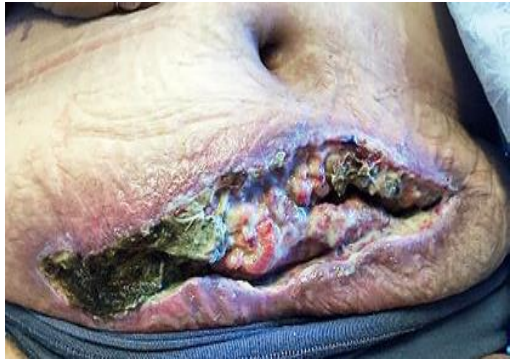
erythema



Induration with dusky discoloration



Multiple plaques



Necrotic ulcer with eschar

How do we describe calciphylaxis?

- Uremic versus non-uremic
- Central versus Peripheral

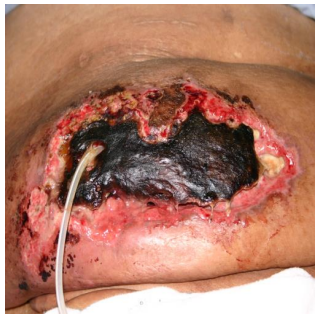
  Central: central areas within subcutaneous tissue such as abdomen, thighs or breasts

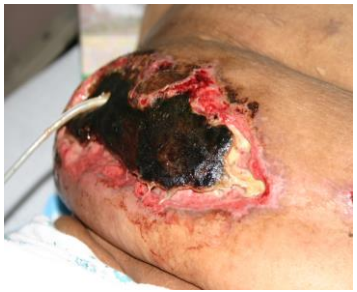
  Peripheral: peripheral sites with limited adipose tissue such as shins or digits

- Ulcerated lesions versus non-ulcerated lesions

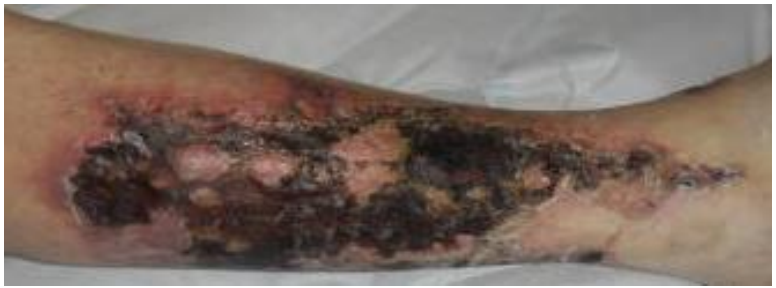
Two cases

- Patient A - 2004
- Patient B -2016





Central calciphylaxis



Peripheral calciphylaxis

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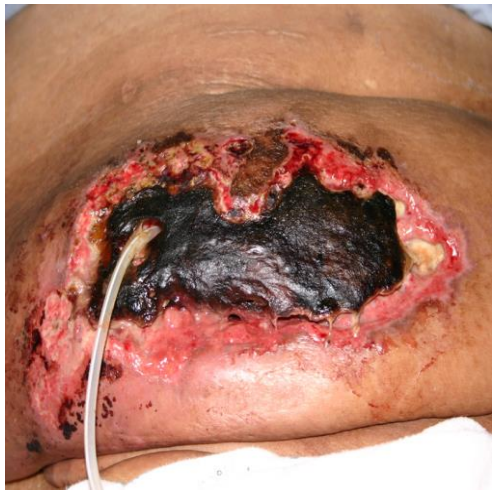
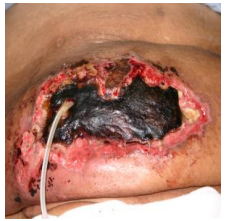
Patient A – central calciphylaxis

- 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

Date/Time	Ca	Mg	Phos
10Feb99 0530	2.16		1.27
04Apr01 1125	1.88	0.69	1.93
06Apr01 1352	1.94	0.77	2.06!
14Jun01 1300	1.62!		2.05!
23Aug01 1325			2.18!
04Oct01 1317			1.54
29Nov01 1107			1.93
31Jan02 1110			1.94
23May02 1135		0.75	2.52!
01Aug02 1230			1.80
05Dec02 1115			1.99
06Mar03 1043			2.45!
29May03 1105			2.08!
21Aug03 1100	2.18		2.52!
07Apr04 1830	2.52	0.84	2.57!



calciphylaxis diagnosed

Takes calcium binders – 1000 elemental calcium TID

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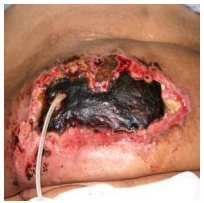
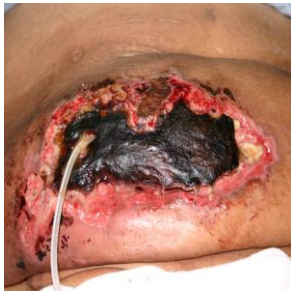
Patient A: CKD-MBD parameters

Date/Time	PTH
04Apr01 1125	53.5
06Apr01 1352	47.0
04Oct01 1317	34.6
23May02 1135	38.6
01Aug02 1230	30.2
06Mar03 1043	39.6
30Dec03 0930	30.5
08Apr04 0605	16.9
20May04 1324	4.9



calciphylaxis diagnosed

Patient A



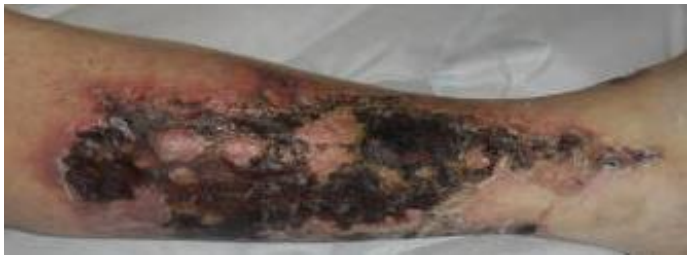
FINAL DIAGNOSIS

UBCUTANEOUS 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

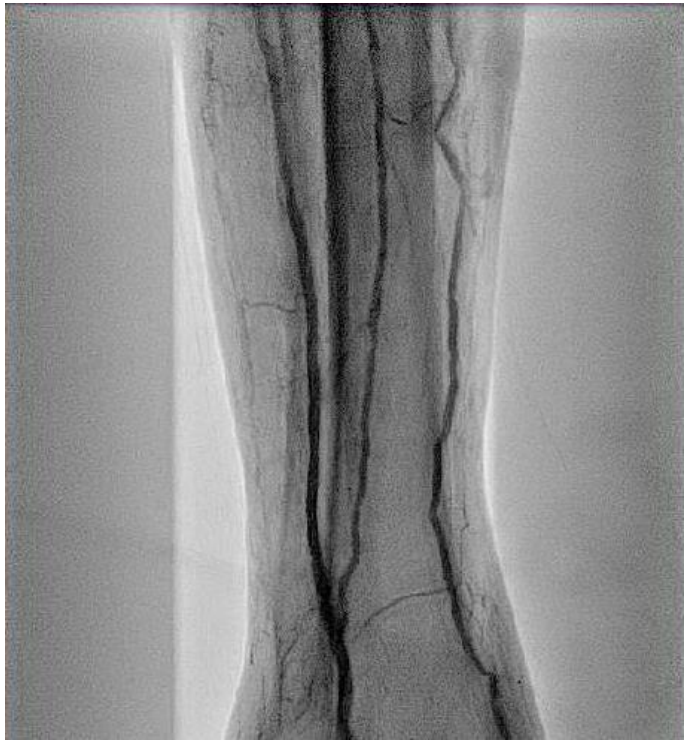
Date/Time	Ca	Mg	Phos
25May15 0925	2.10	0.66	1.02
17Aug15 0945	1.99	0.51	1.09
12Oct15 0525	2.02	0.51	1.65
12Oct15 1740	1.95	0.95	1.82
09Nov15 1040	2.04	0.56	1.03
16Dec15 0235	1.59!	0.73	0.97
16Dec15 0756	1.71	0.71	1.05
16Dec15 1505	1.81	0.71	1.01
17Dec15 0935	1.91	0.58	0.85
20Dec15 0700	2.02	0.49!	0.72
20Dec15 1845	1.97	1.29	0.77
21Dec15 0753	2.04	0.80	0.82
22Dec15 0702	1.92	0.77	0.71
18Jan16 1050	2.07	0.71	0.73
31Mar16 0950		0.67	0.88
11Apr16 1125	2.06	0.80	0.80
13Apr16 1210	2.03	0.73	0.65
14Apr16 1135	2.02	0.69	0.98
15Apr16 0040	1.95	0.61	0.85
09May16 1230	2.05	0.77	0.87

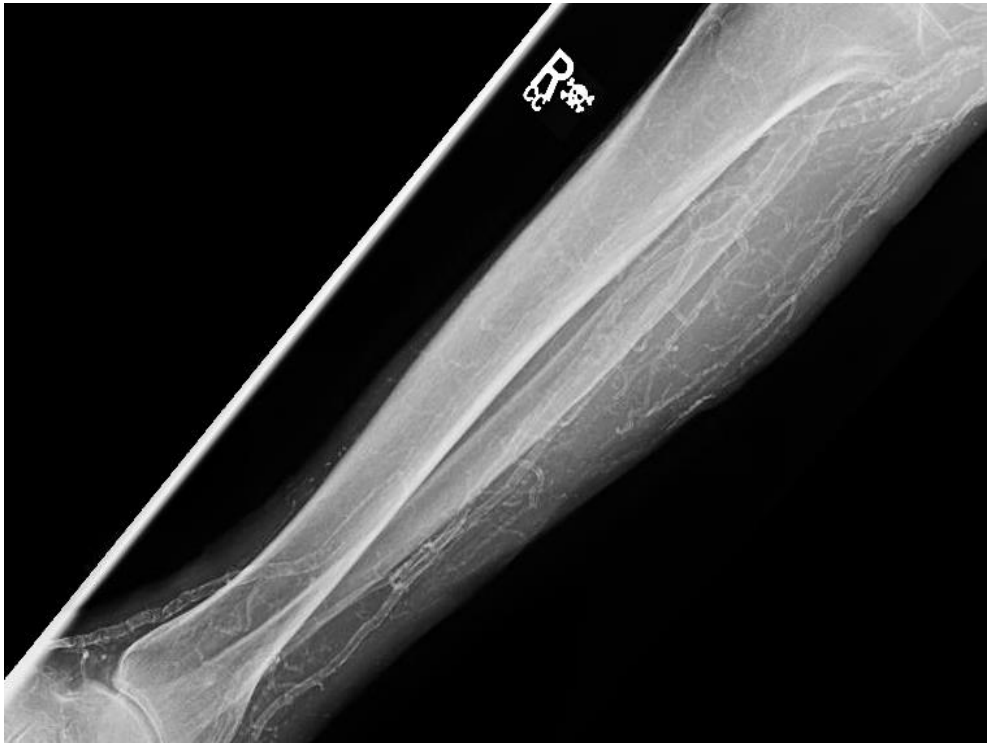
Warfarin started for AF

Date/Time	PTH
25May15 0925	35.6
17Aug15 0945	76.2
09Nov15 1040	46.0
18Jan16 1050	102.4
31Mar16 0950	87.7
11Apr16 1125	101.0
09May16 1230	26.3

Calcitriol started

calciphylaxis diagnosed

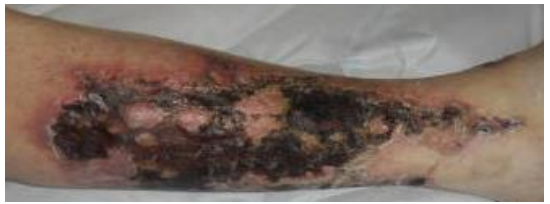



R

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*‡

J Am Soc Nephrol 27: 3421–3429, 2016.

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Who is at risk? Demographics

Characteristic	Cases (*n*=1030)	Controls (*n*=2060)	*P* Value
Comorbidities and vital signs			
Diabetes mellitus, %	61	44	<0.001
Obesity, %	65	42	<0.001
Weight, kg	101.2±29.3	82.0±25.5	<0.001
BMI, kg/m^2	36.7±10.2	30.3±8.5	<0.001
Systolic BP, mmHg	150±31	148±27	0.04
Diastolic BP, mmHg	78±18	78±17	0.66

J Am Soc Nephrol 27: 3421–3429, 2016.

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Who is at risk?
CKD-MBD parameters + treatments

Characteristic	Cases (*n*=1030)	Controls (*n*=2060)	*P* Value
Mineral bone parameters and therapies			
Serum calcium (albumin corrected), mg/dl	9.1±0.8	9.0±0.8	0.04
Serum phosphorus, mg/dl	4.9±2.3	4.6±2.0	0.001
Serum PTH, pg/ml	379 (184, 651)	250 (100, 471)	<0.001
Serum ALP, U/L	116.6±87.5	106.8±74.3	0.002
Serum 25-hydroxyvitamin D, ng/ml	19.4±10.1	16.7±11.2	0.07
Dialysate calcium, mmol/L	2.5±0.3	2.5±0.2	0.20
Nutritional vitamin D treatment, %	9	5	<0.001
Activated vitamin D treatment, %	32	37	0.02
Cinacalcet treatment, %	7	2	<0.001
Phosphate-binding agent treatment, %	35	31	0.01

Who is at risk?
Other medications

Characteristic	Cases (*n*=1030)	Controls (*n*=2060)	*P* Value
Serum albumin, g/dl	3.5±0.5	3.5±0.6	0.49
Hemoglobin, g/dl	10.2±1.5	10.4±1.5	0.01
Serum bicarbonate, mEq/L	22.5±3.9	22.5±4.0	0.61
sPKtV	1.5±0.4	1.6±0.4	<0.001
Warfarin treatment, %	14	4	<0.001
Statin treatment, %	25	22	0.04
ESA treatment, %	45	56	<0.001
ACEi/ARB treatment, %	15	13	0.22

J Am Soc Nephrol 27: 3421–3429, 2016.

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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 2. Differential Diagnosis of Calciphylaxis.

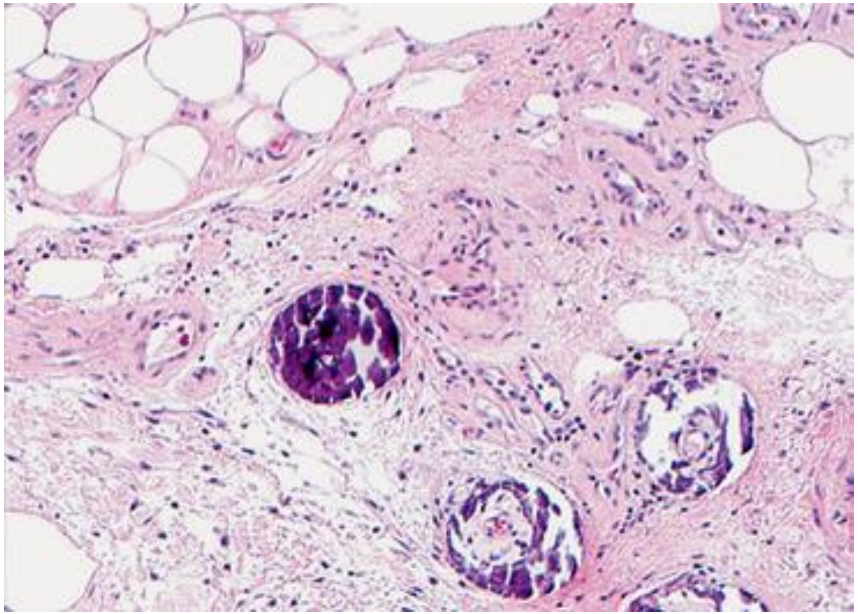
Warfarin-induced skin necrosis
Atherosclerotic vascular disease
Venous stasis ulcer
Cellulitis
Cholesterol embolization
Dystrophic calcinosis cutis
Livedoid vasculopathy
Nephrogenic systemic fibrosis
Oxalosis
Pyoderma gangrenosum
Purpura fulminans
Necrotizing vasculitis
Martorell's ulcer

N ENGL J MED 378;18

What is the pathology of calciphylaxis?

Classic histologic features

- Calcification
- Fibrointimal hyperplasia
- Thrombosis



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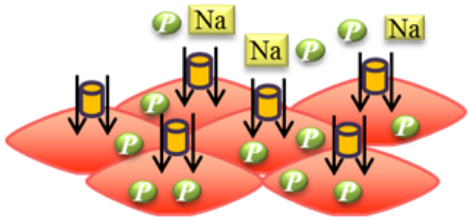
Calcification

- 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



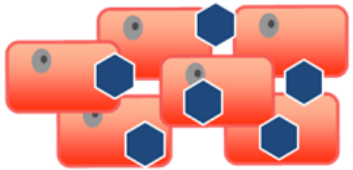
VSMCs

Shobeiri, N. 2013. *The Pathogenesis of Vascular Calcification in Chronic Kidney Disease: Consequences and Treatments.* (Doctoral Thesis). Retrieved from QSpace.

Mechanisms of micro-vessel calcification

Phosphate uptake
by PiT-1 and PiT-2

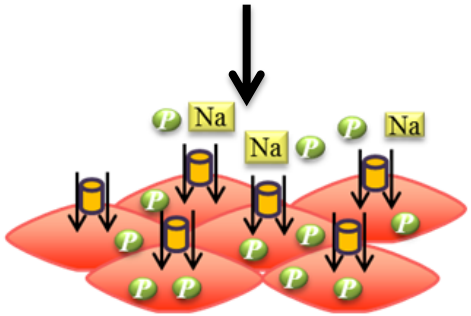
VSMCs



Calcifying VSMCs

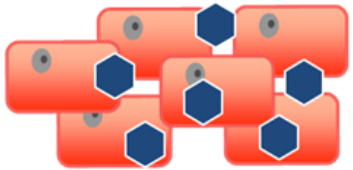
Mechanisms of micro-vessel calcification

Phosphate uptake
by PiT-1 and PiT-2



VSMCs

Runx2



Calcifying VSMCs

Mechanisms of micro-vessel calcification

Phosphate uptake
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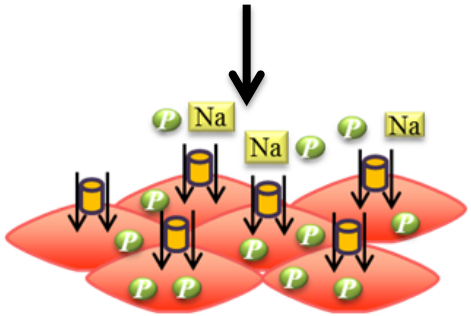


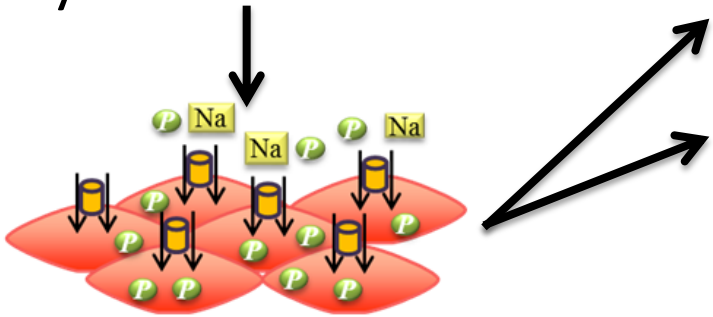
VSMCs

Osteoblastic Transdifferentiation

- Osteoblasts are bone forming cells
- Secrete bone matrix proteins

Mechanisms of micro-vessel calcification

Phosphate uptake
by PiT-1 and PiT-2



VSMCs

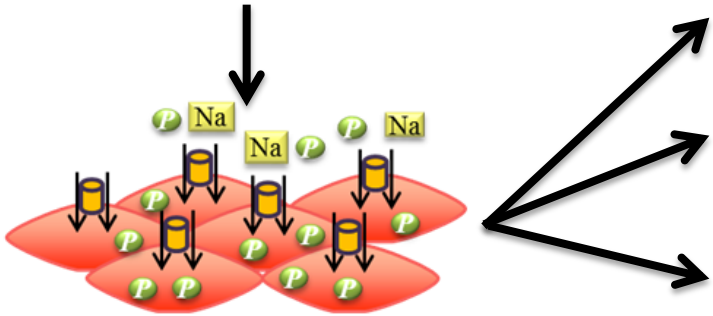
Osteoblastic
Transdifferentiation

Nidus Formation

- Apoptotic Bodies
- Elastin matrix Degradation
- Matrix Vesicles

Mechanisms of micro-vessel Calcification

Phosphate uptake
by PiT-1 and PiT-2



VSMCs

Osteoblastic
Transdifferentiation

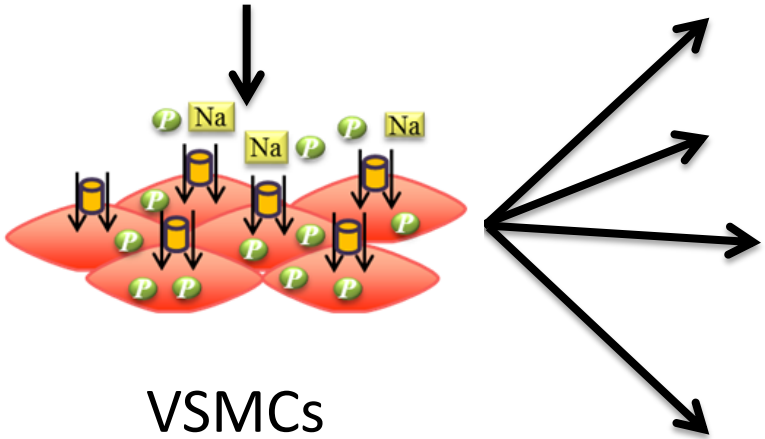
Nidus Formation

Promoters of Vascular Calcification

- Phosphate
- Calcium

Mechanisms of micro-vessel Calcification

Phosphate uptake
by PiT-1 and PiT-2



VSMCs

Osteoblastic
Transdifferentiation

Nidus Formation

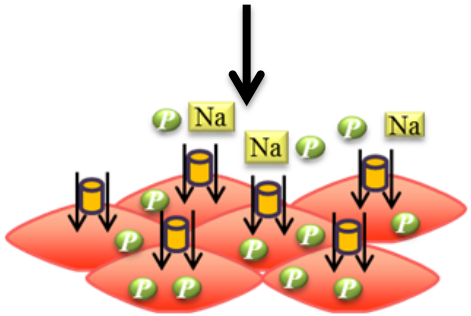
Promoters of Vascular Calcification

Inhibitors of Vascular Calcification

- Matrix Gla Protein
- Fetuin-A
- Magnesium

Mechanisms of Vascular Calcification

Phosphate uptake by PiT-1 and PiT-2



VSMCs

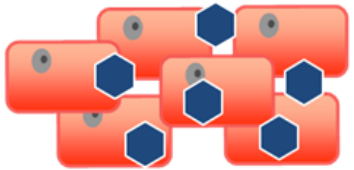
Osteoblastic Transdifferentiation

Nidus Formation

Inhibitors of Vascular Calcification

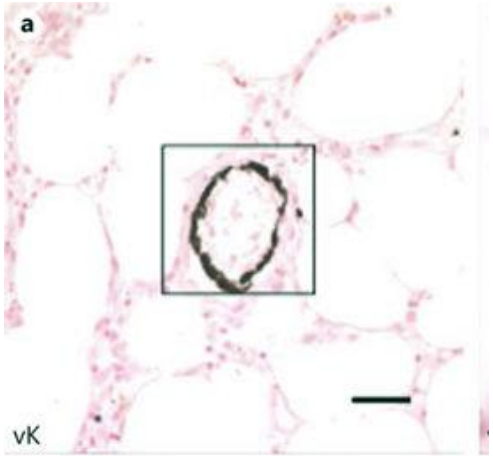
Promoters of Vascular Calcification

Tissue-Specific Mechanisms

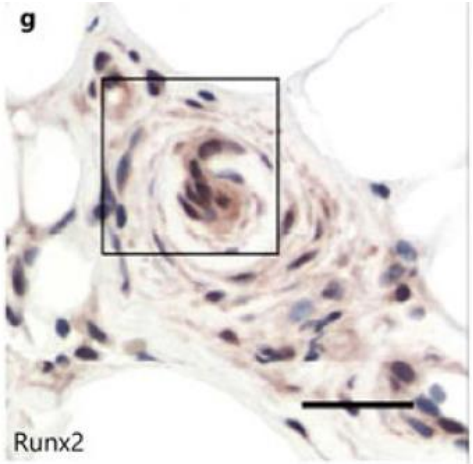


Calcifying VSMCs

Calcification in arterioles in clinical calciphylaxis



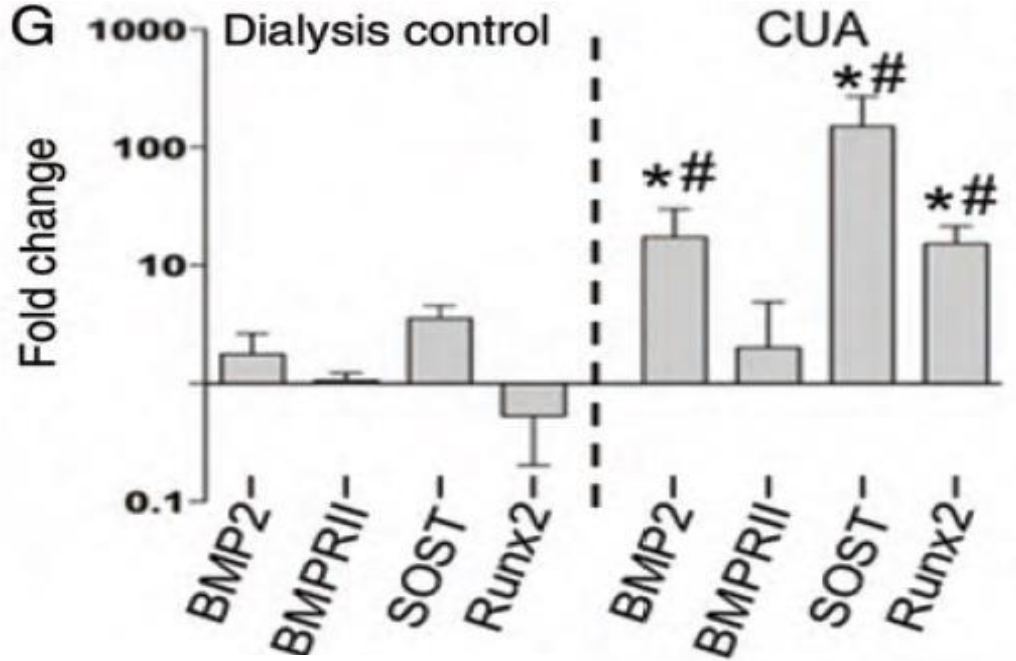
Calcification in arteriole



Up-regulation of Runx2

Am J Nephrol. 2017 ; 46(5): 429–438.

Calciphylaxis – osteogenic phenotype



Nephrol Dial Transplant (2013) 28: 856–868

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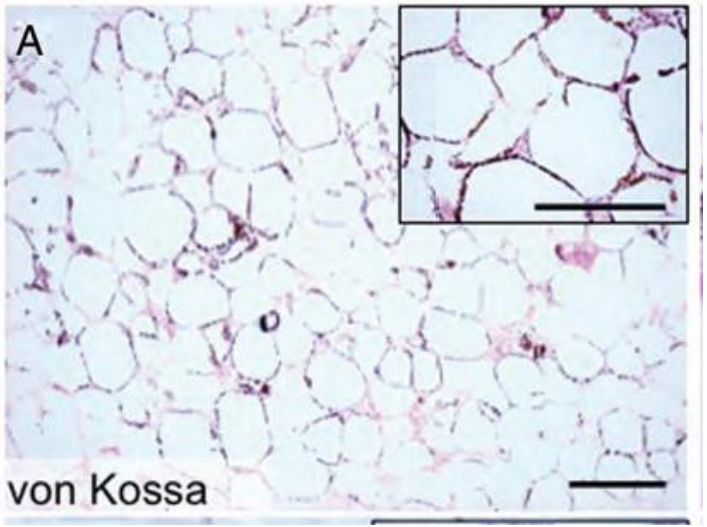
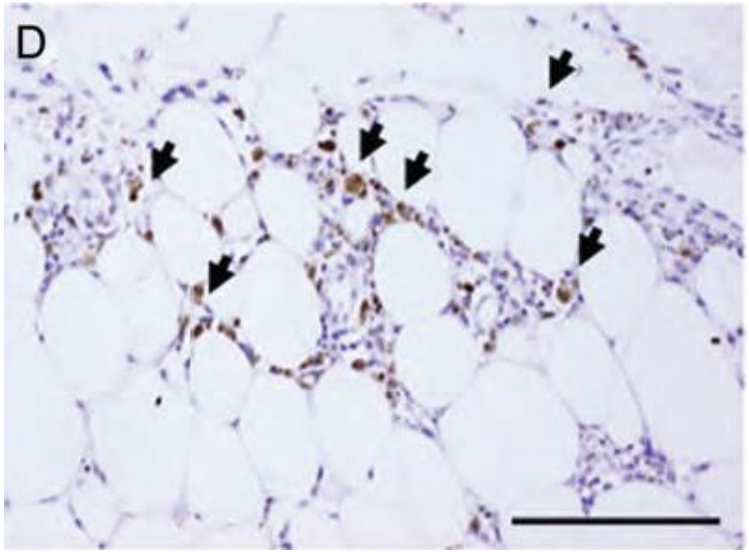
Adipocytes calcify in calciphylaxis



Calcification of adipocytes



BMP-2 staining of adipocytes

Nephrol Dial Transplant (2013) 28: 856–868

Obesity

Adipocyte induced arterial calcification is prevented with sodium thiosulfate

Neal X. Chen [a,*], Kalisha O'Neill [a], Nader Kassis Akl [a], Sharon M. Moe [a,b]

[a] *Divison of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA*
[b] *Roudebush VA Medical Center, Indianapolis, IN, USA*

N.X. Chen et al. / Biochemical and Biophysical Research Communications 449 (2014) 151–156

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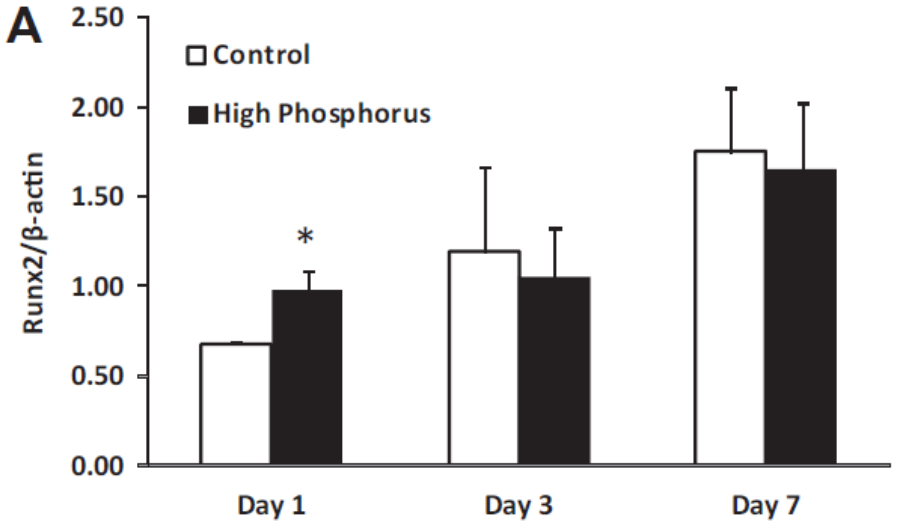
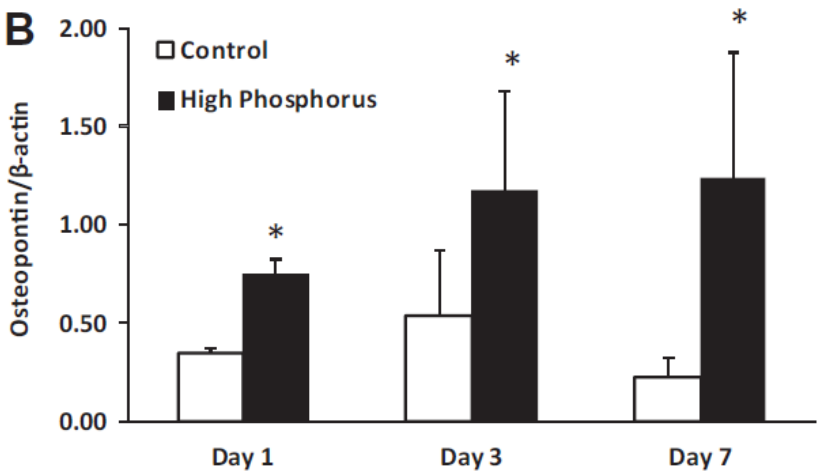
Adipocytes express the ‘osteogenic program’





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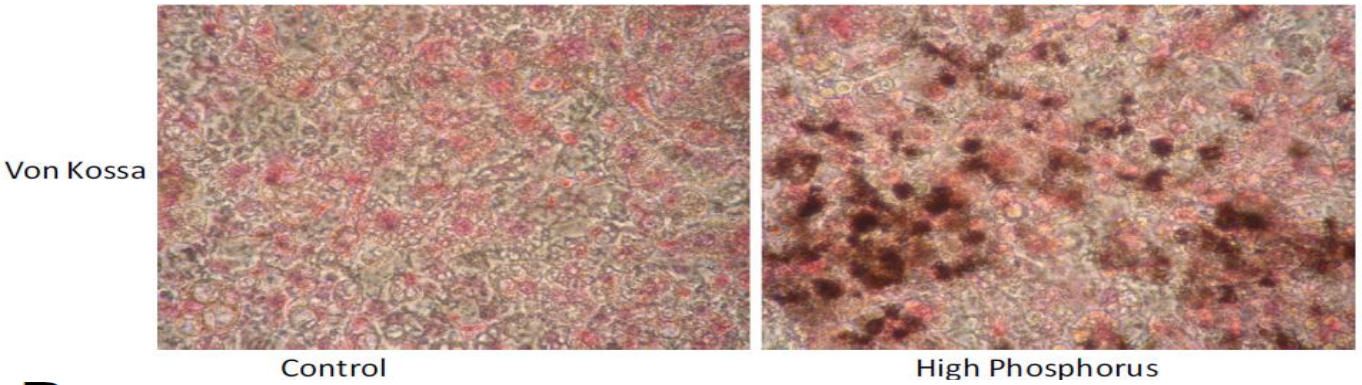
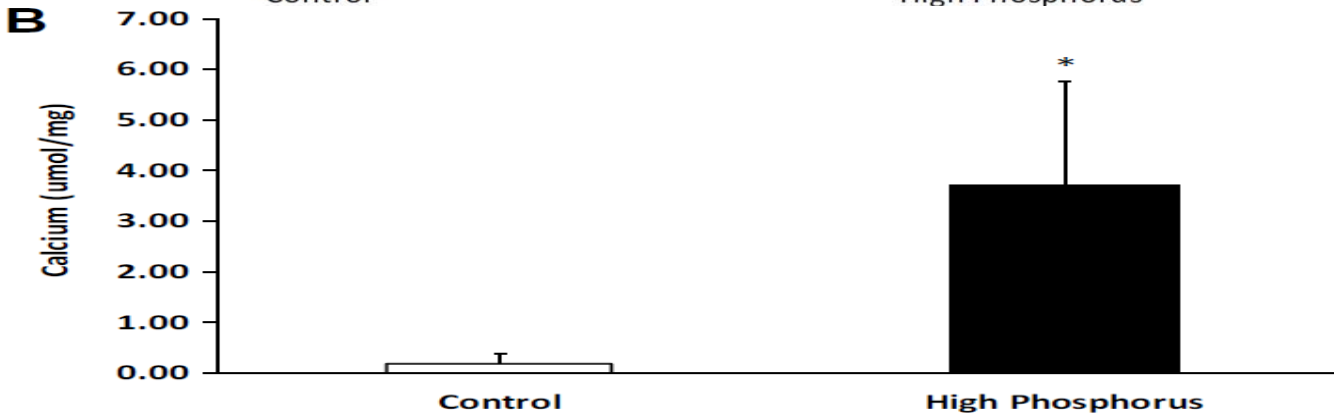
Mature adipocytes exposed to high phosphate media calcify





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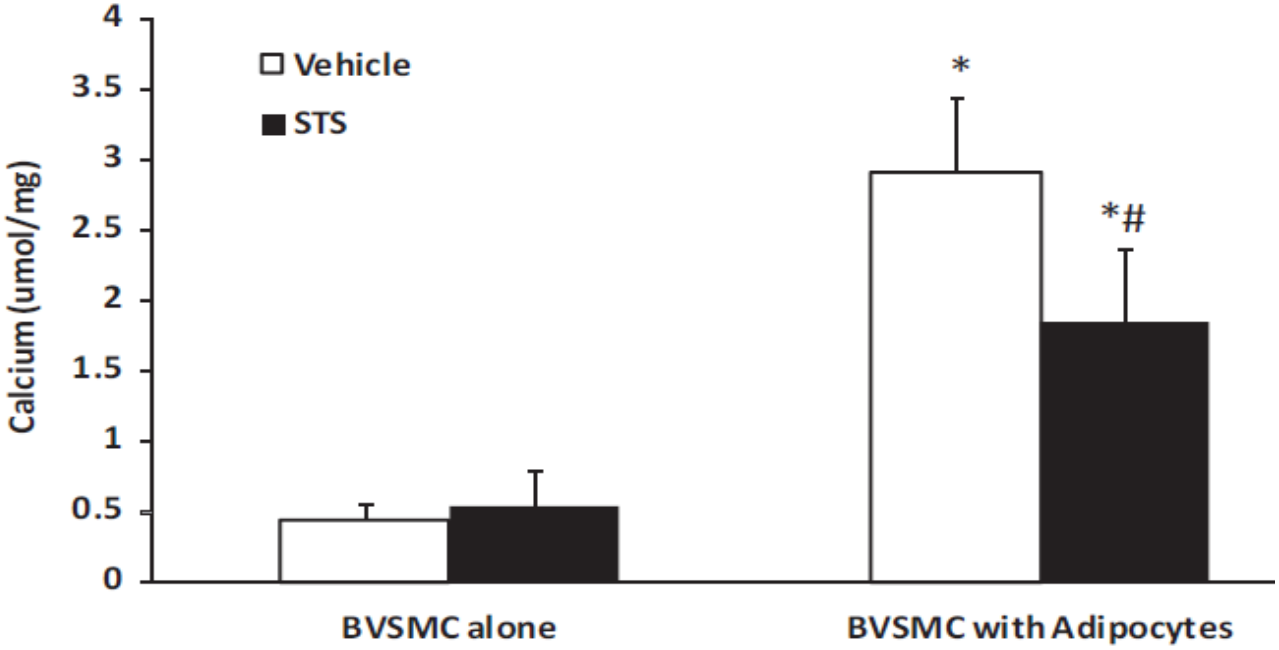
Adipocytes enhance calcification of VSMCs



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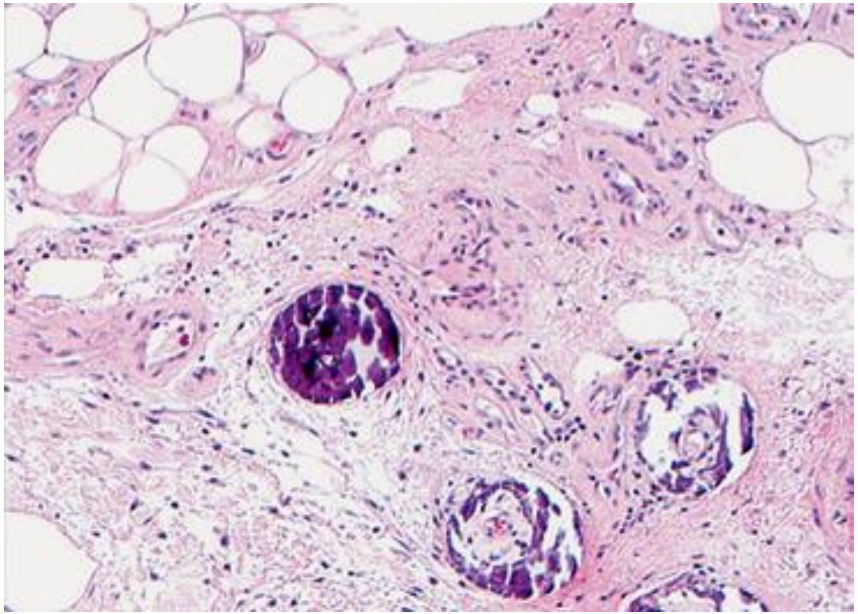
Pathology of calciphylaxis

Histologic features

- Calcification
- Fibrointimal hyperplasia
- thrombosis



How specific are these histologic findings for calciphylaxis?

Questionable specificity of histologic findings in calcific uremic arteriolopathy

Check for updates

see commentary on page 244

Carla L. Ellis[1] and W. Charles O'Neill[2]

[1]Department of Pathology, Emory University School of Medicine, Atlanta, Georgia, USA; and [2]Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

Kidney International (2018) **94,** 390–395

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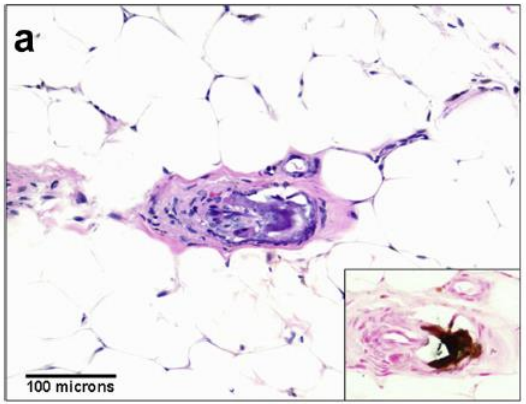
Table 1 | Patient characteristics

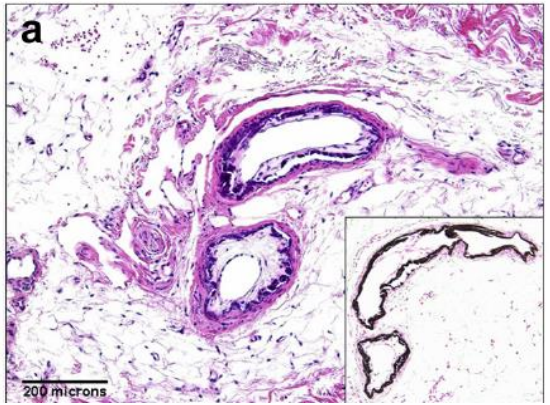
	Amputations	Skin biopsies	*P* Value
N	34	37	
Age (mean ± SEM)	62 ± 1.9	53 ± 2.5	0.006
Gender (% female)	29	81	<0.0001
Diabetes (%)	71	51	0.14
ESRD (%)	100	78	0.005
Dialysis	91	76	
Transplantation	9	3	
Warfarin use (%)	21	49	0.02

ESRD, end-stage renal disease.

How specific is a finding of vascular calcification in a skin biopsy?



Healthy skin in patient with ESKD

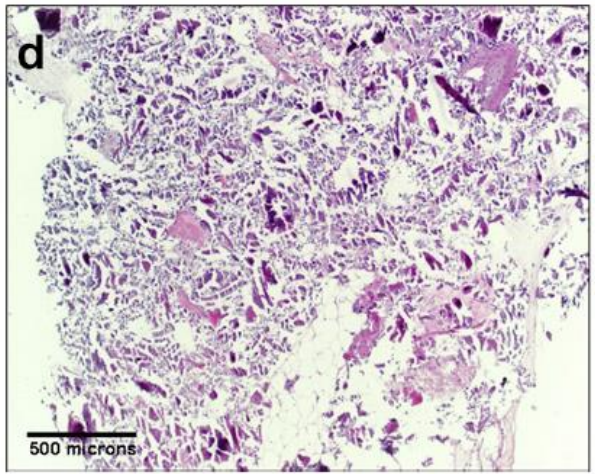


Suspected calciphylaxis

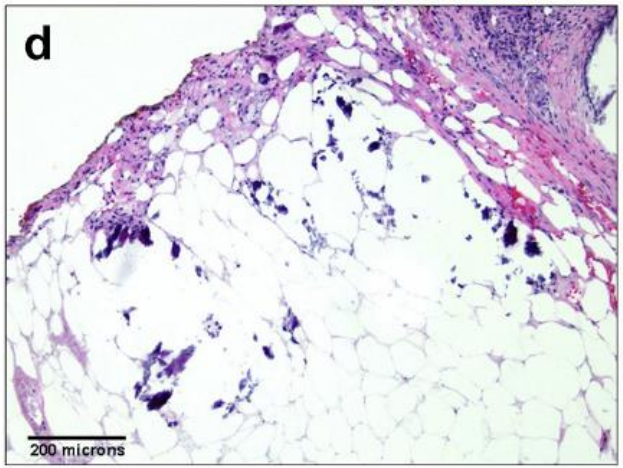
Prevalence of VK positive calcification was similar between skin biopsies performed for suspicion of calciphylaxis and healthy skin from amputation margins

Kidney International (2018) **94,** 390–395

How specific is a finding of calcification of the subcutaneous fat in a skin biopsy?



Healthy skin in patient with ESKD

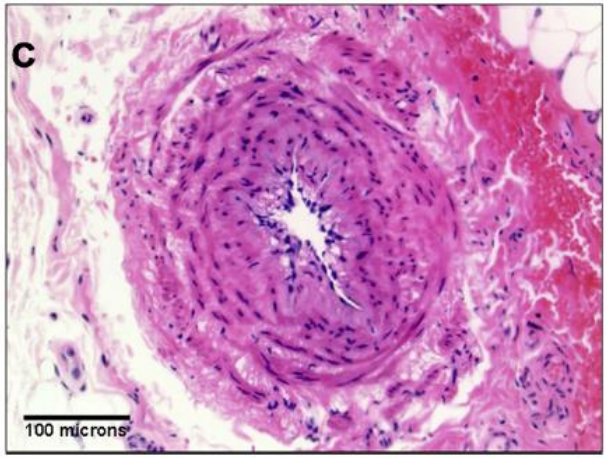


Suspected calciphylaxis

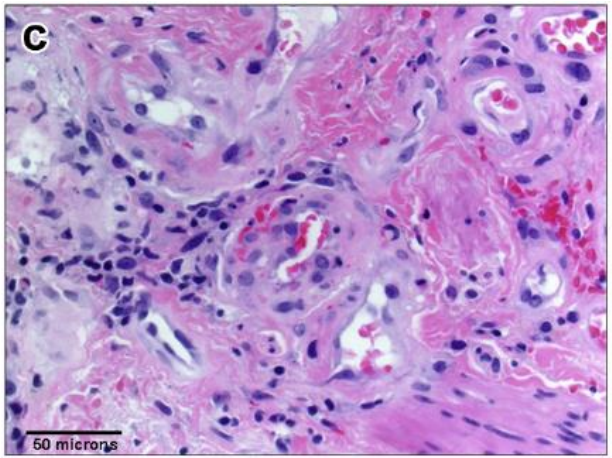
Prevalence of extravascular soft tissue calcification was not different

Kidney International (2018) **94,** 390–395

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

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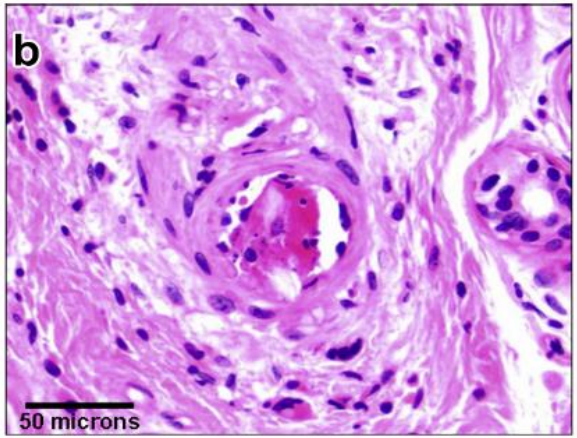
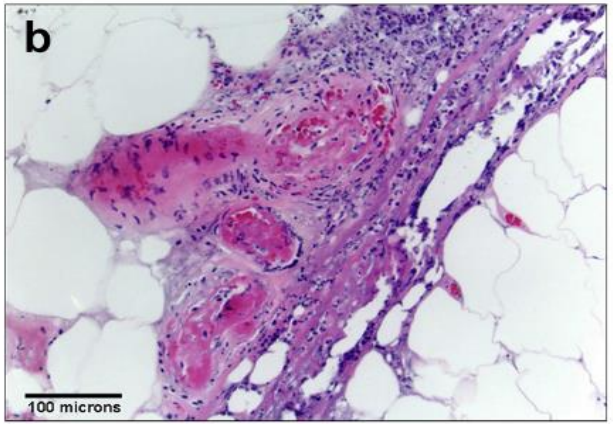
How specific is a finding of arterial thrombosis in a skin biopsy?



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’

Kidney International (2018) **94,** 390–395

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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Triggers: Vitamin K status

Characteristic	Cases (*n*=1030)	Controls (*n*=2060)	*P* Value
Serum albumin, g/dl	3.5±0.5	3.5±0.6	0.49
Hemoglobin, g/dl	10.2±1.5	10.4±1.5	0.01
Serum bicarbonate, mEq/L	22.5±3.9	22.5±4.0	0.61
sPKtV	1.5±0.4	1.6±0.4	<0.001
Warfarin treatment, %	14	4	<0.001
Statin treatment, %	25	22	0.04
ESA treatment, %	45	56	<0.001
ACEi/ARB treatment, %	15	13	0.22

J Am Soc Nephrol 27: 3421–3429, 2016.

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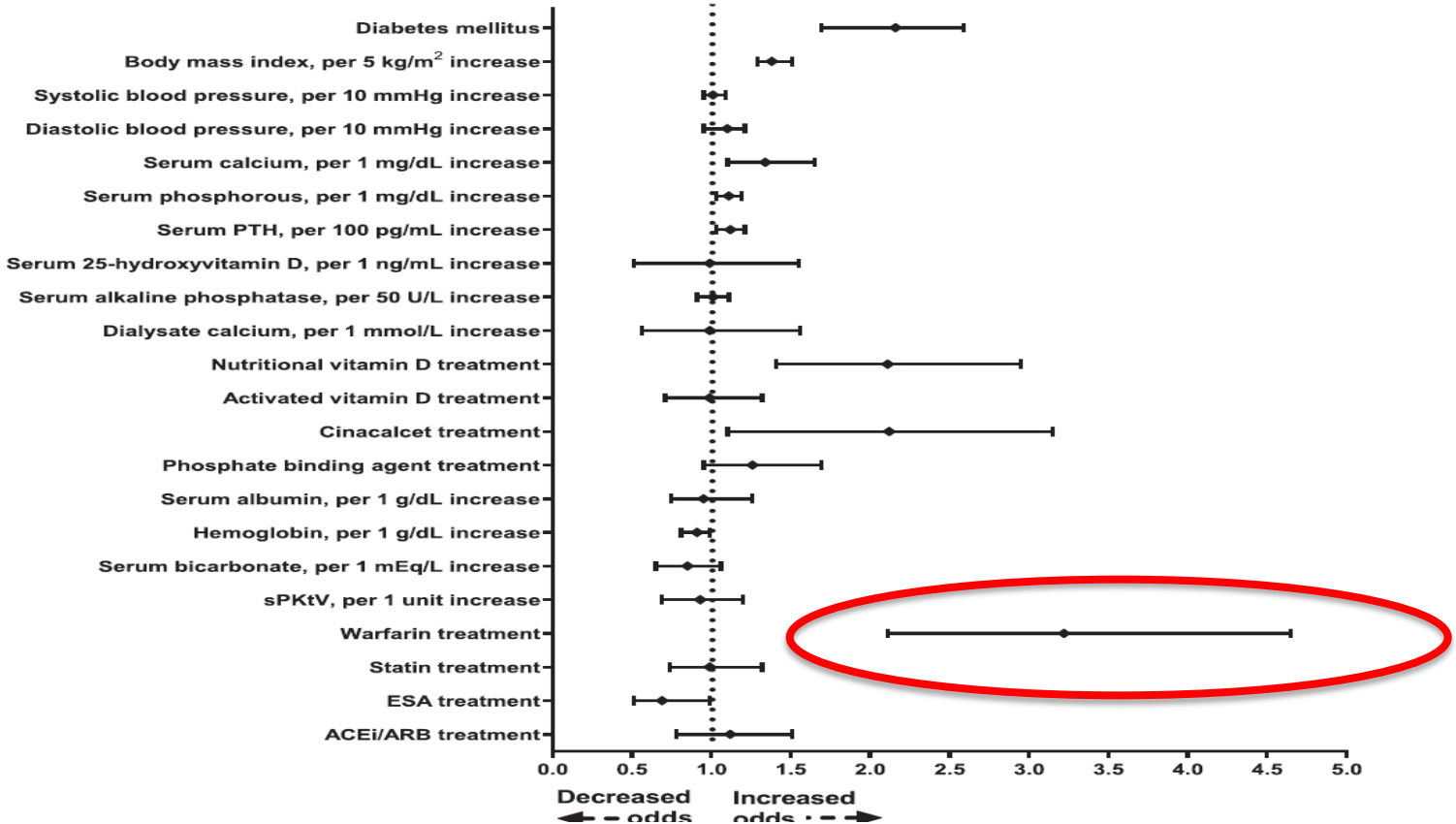

J Am Soc Nephrol 27: 3421–3429, 2016.

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Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry

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

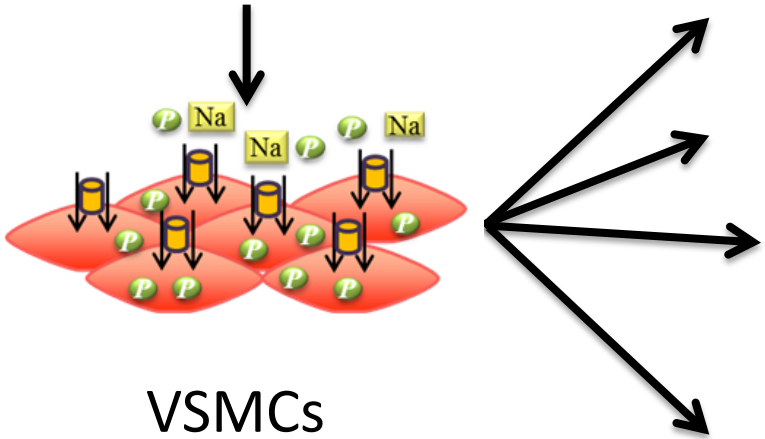
Table 3. Medication use in the group of dialysis patients at the time of CUA development[a]

Medication[a]	All HD/HDF, patients, $n = 193$		PD, $n = 25$	
	Yes	No	Yes	No
Active vitamin D (calcitriol, paricalcitol, others)	102 (53%)	87 (45%)	15 (60%)	9 (36%)
Cinacalcet	50 (26%)	137 (71%)	12 (48%)	12 (48%)
Any phosphate binder (PB)[b]	149 (77%)	41 (21%)	20 (80%)	4 (16%)
Calcium-containing PB[b]			11 (44%)	
Sevelamer[b]			7 (28%)	
Lanthanum carbonate[b]			1 (4%)	
Other PB[b]			2 (8%)	
VKAs	98 (51%)	93 (48%)	15 (60%)	9 (36%)
Erythropoietin and other Erythropoiesis-stimulating agents, ESAs	160 (83%)	29 (15%)	21 (84%)	2 (8%)

Nephrol Dial Transplant (2017) 32: 126–132

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

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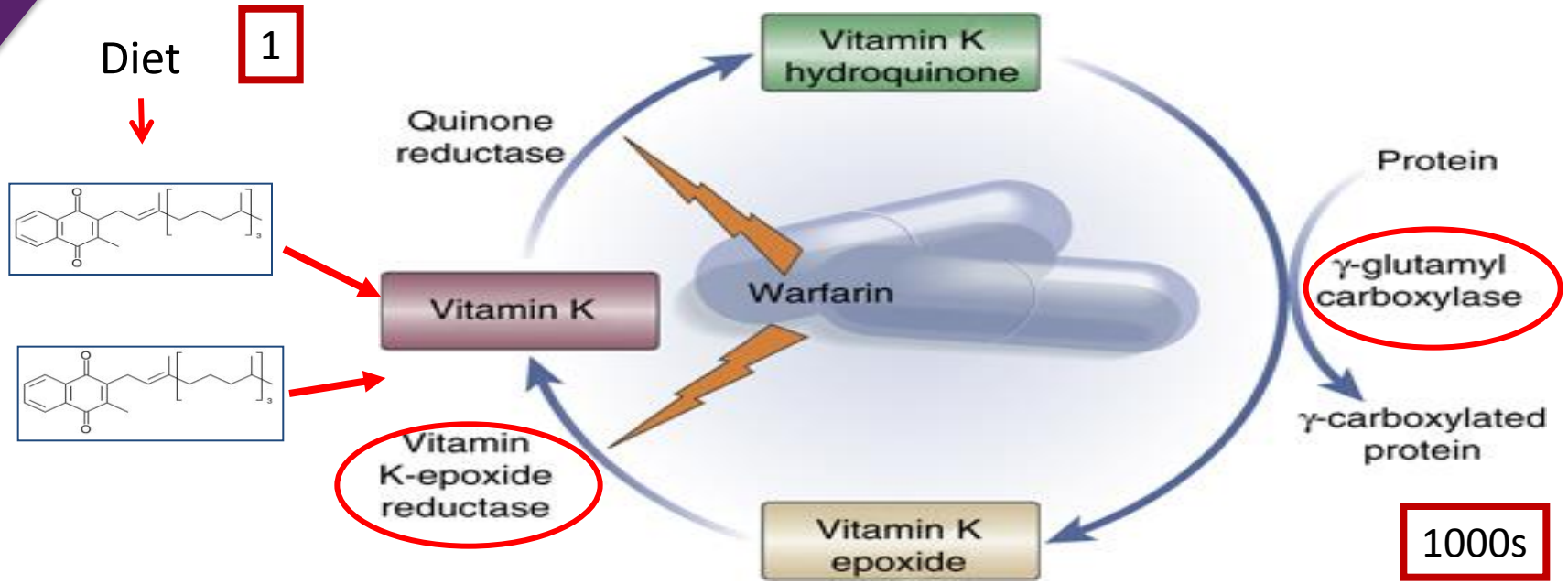
Vitamin K cycle



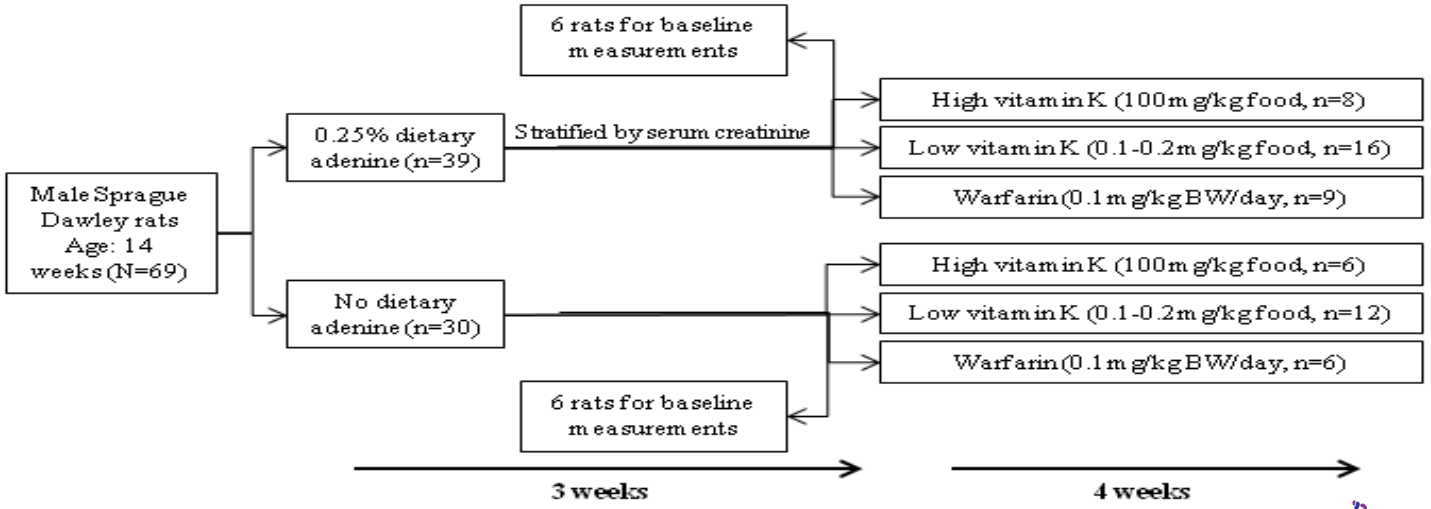
Uncarboxylated MGP (inactive) → **Vitamin K** dependent carboxylation → **Carboxylated MGP** (active) → Via **BMP-2 inhibition** (−) → **Arteriolar calcification in CUA**

http://www.kidney-international.org

see commentary on page 782

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

Kristin M. McCabe[1], Sarah L. Booth[2], Xueyan Fu[2], Navid Shobeiri[1], Judith J. Pang[1], Michael A. Adams[1] and Rachel M. Holden[3]



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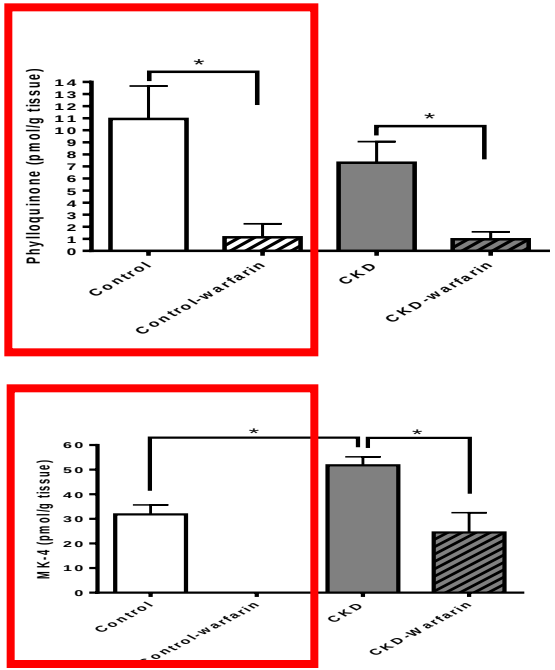
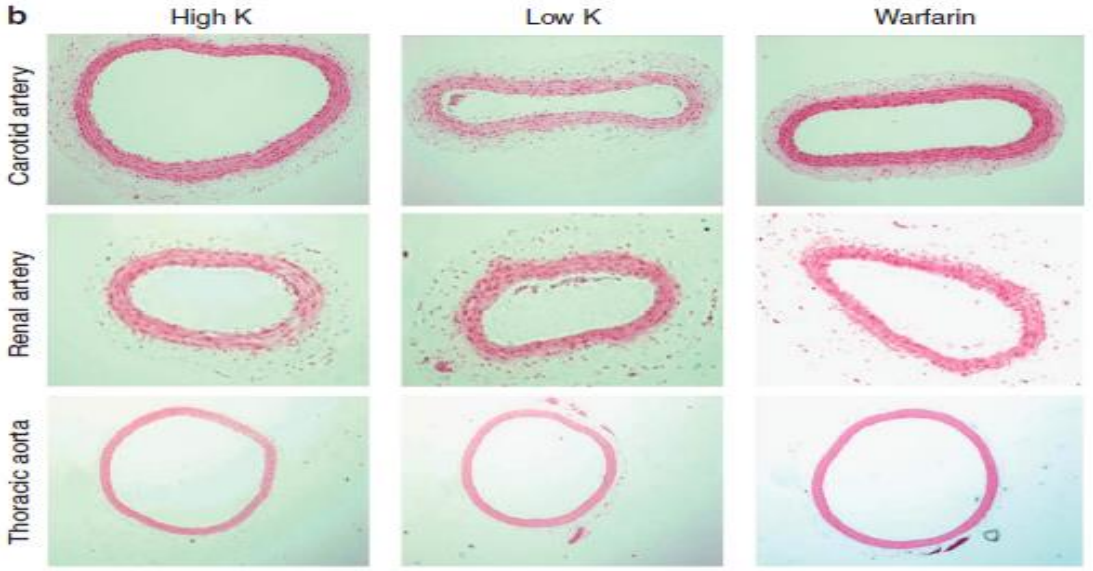
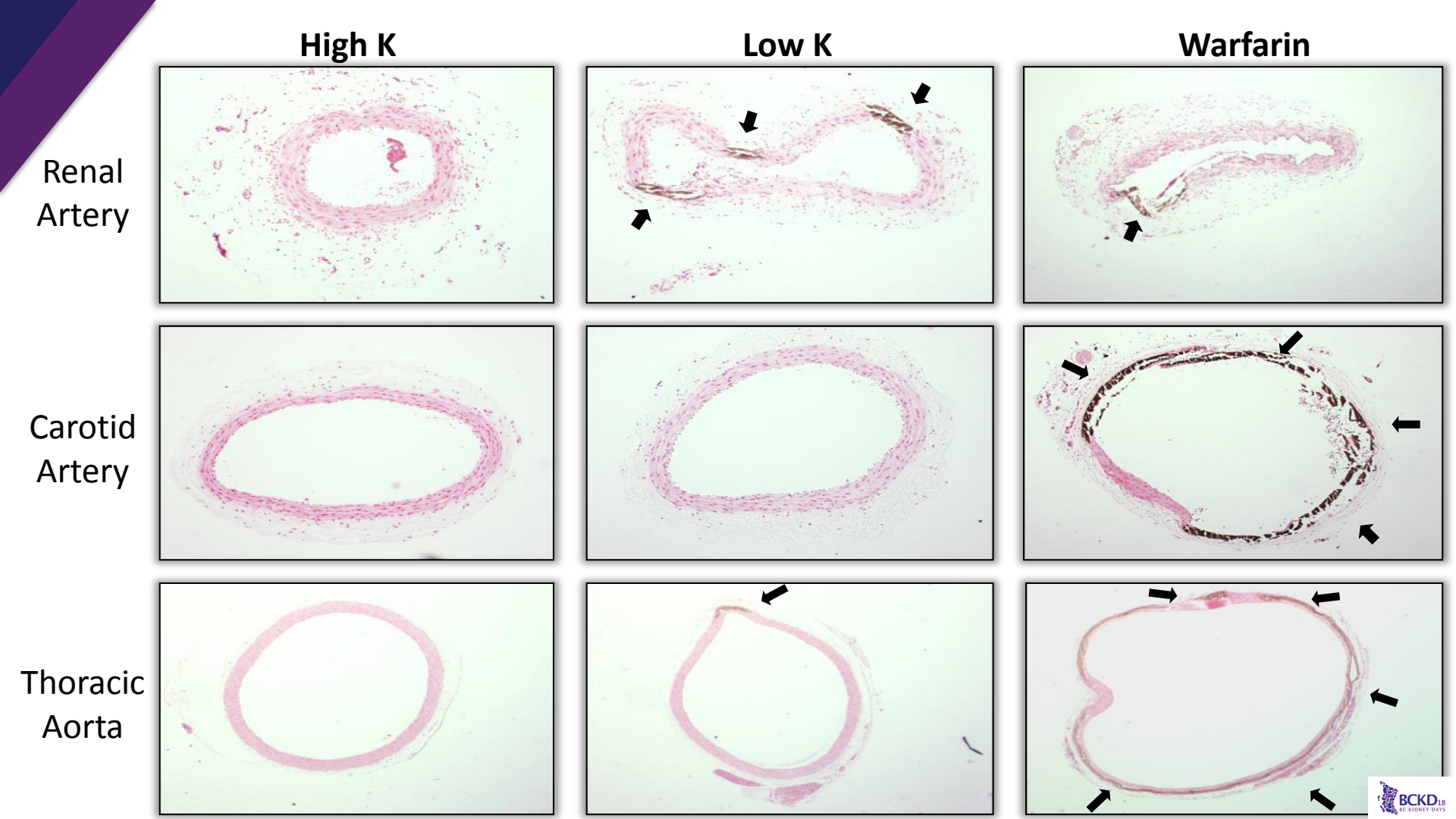
Warfarin lowered tissue vitamin K levels but did not cause VC in healthy rats

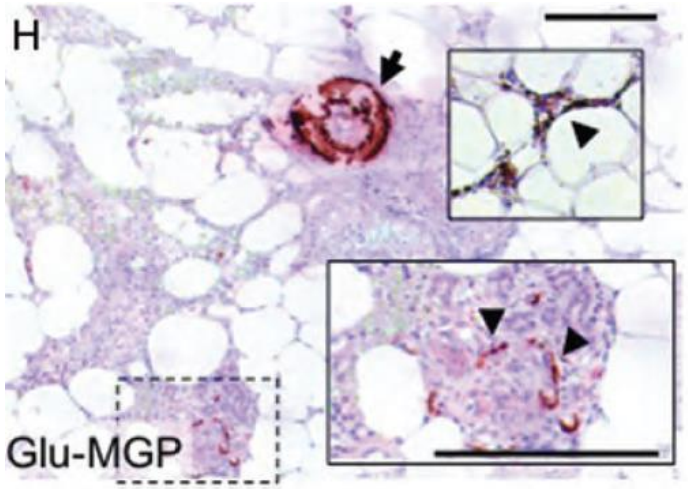




Healthy rats


High K
Low K
Warfarin
Renal Artery
Carotid Artery
Thoracic Aorta

Triggers: Vitamin K

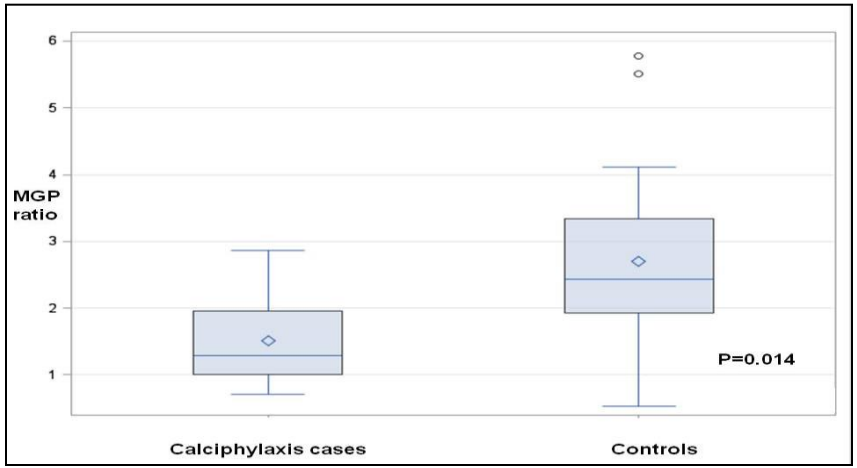


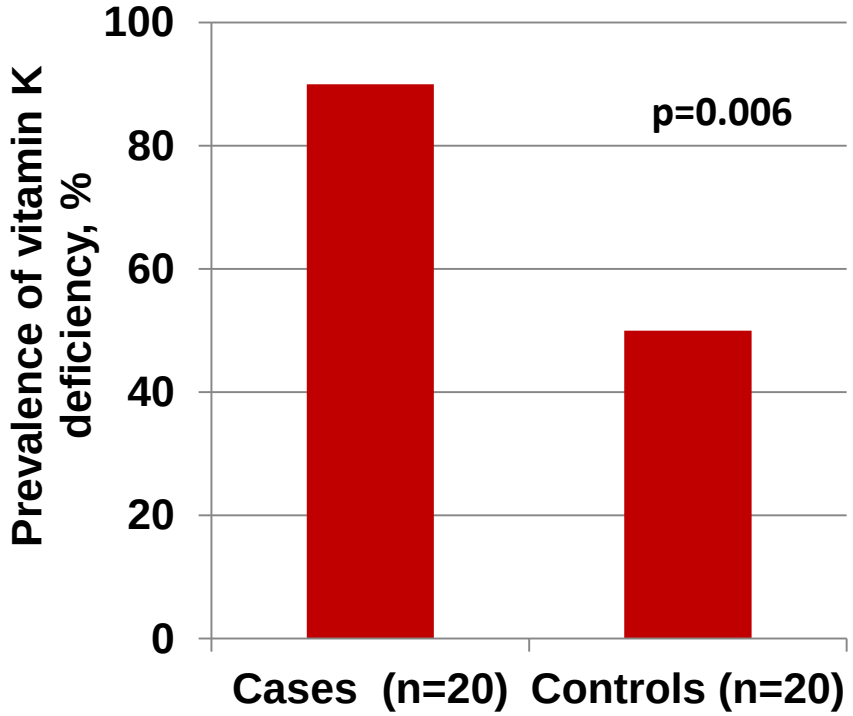
Calciphylaxis characterized by relative reductions in carboxylated MGP and elevated uncarboxylated MGP in biopsy samples

Nephrol Dial Transplant (2013) 28: 856–868

Calciphylaxis patients have low VK status

Characteristics	Cases (n=20)	Controls (n=20)	P value
Age, years	58 ± 16	62 ± 14	NA
Female gender, %	35	35	NA
Non-White race, %	10	10	NA
Warfarin therapy, %	30	30	NA



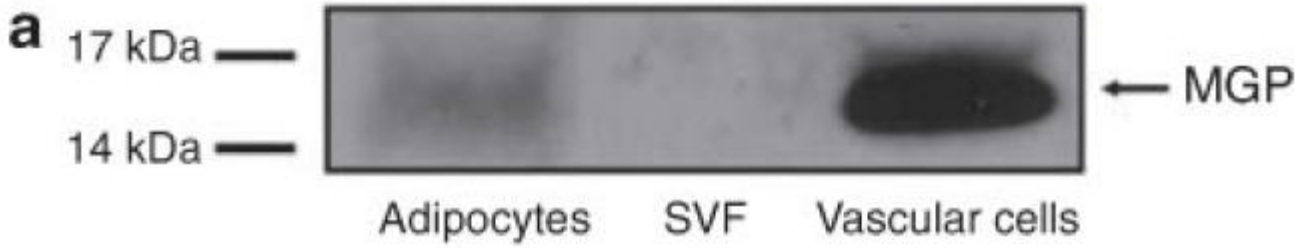


With permission Nigwekar, Malhotra, and Booth. J Am Soc Nephrol, 2017

Adipocytes secrete MGP

Using gene expression to predict the secretome of differentiating human preadipocytes

DM Mutch[1,2,3,5], C Rouault[1,2,3], M Keophiphath[1,2,3], D Lacasa[1,2,3] and K Clément[1,2,3,4]



MGP protein detected in the secretion media of adipocytes

International Journal of Obesity (2009) 33, 354–363

Triggers: Trauma

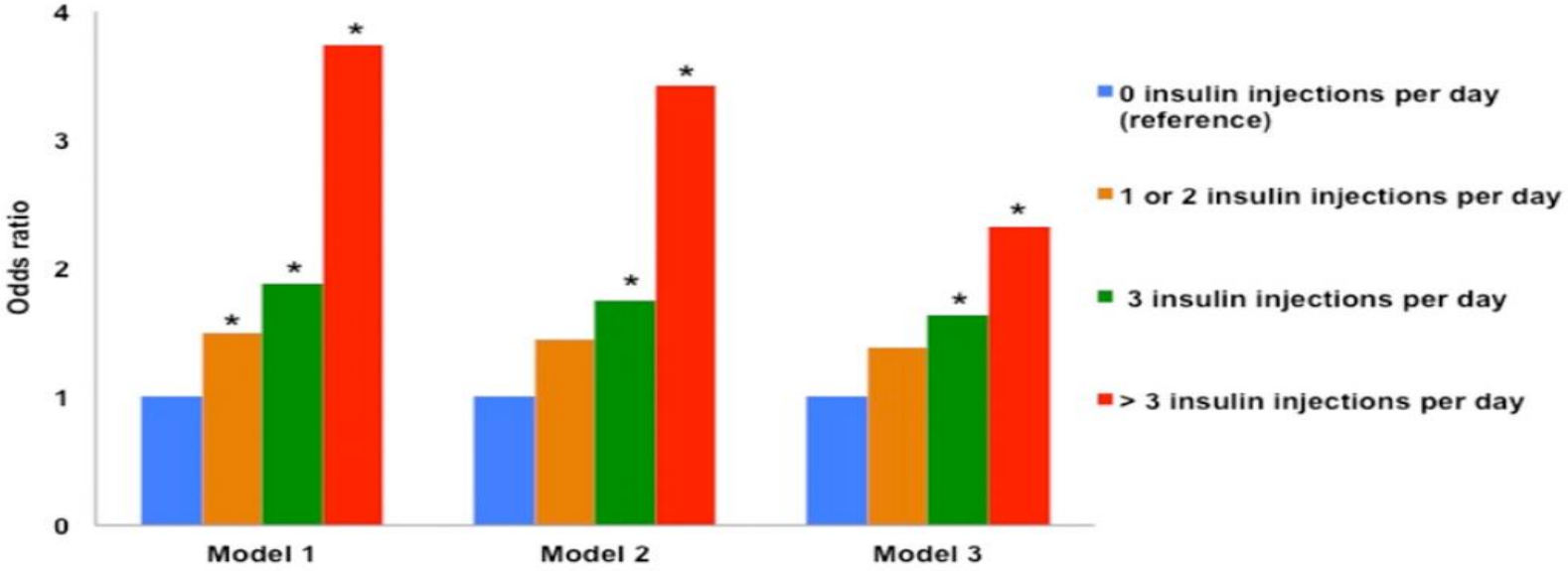


Figure 2. ORs of future CUA involving lower abdomen and/or upper thigh areas by number of insulin injections per day at hemodialysis initiation. Model 1 is an unadjusted model; model 2 is adjusted for age, race, and sex; model 3 is adjusted for covariates

J Am Soc Nephrol 27: 3421–3429, 2016.

Triggers: Thrombophilia

JAMA Dermatology | Original Investigation

Association Between Hypercoagulable Conditions and Calciphylaxis in Patients With Renal Disease

A Case-Control Study

JAMA Dermatol. 2018;154(2):182-187. d

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Table 3. Hypercoagulability Laboratory Values Restricted to Patients With Stage 5 Chronic Kidney Disease (CKD5)[a]

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

JAMA Dermatol. 2018;154(2):182-187. d

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 Rothe[1,2*], Vincent Brandenburg[3], Margot Haun[4], Barbara Kollerits[4], Florian Kronenberg[4], Markus Ketteler[1], Christoph Wanner[2]

- 144 HD patients from the German calciphylaxis registry were compared with 370 dialysis patients without calciphylaxis
- Investigation of 10 target genes

PLOS ONE | DOI:10.1371/journal.pone.0172407 February 17, 2017

Triggers: genetic predisposition

Gene encoding	SNP	OR[§]	95% confidence interval	P value
CD73	Rs9444348	1.48	1.11–1.97	0.008
FGF23	Rs12812339	0.58	0.38–0.87	0.009
FGF23	Rs7310492	1.49	1.06–2.09	0.021
CD73	Rs4431401	1.71	1.08–2.71	0.023
VDR	Rs10783223	0.73	0.55–0.96	0.025
VDR	Rs17882106	1.65	1.06–2.56	0.026
FGF23	Rs6489536	0.70	0.51–0.96	0.026
FGF23	Rs11063118	1.41	1.03–1.92	0.032
FGF23	Rs13312747	1.50	1.01–2.25	0.047

Calciphylaxis – other potential triggers

- Autoimmune disorders
- Recurrent hypotension
- Vitamin D analogues

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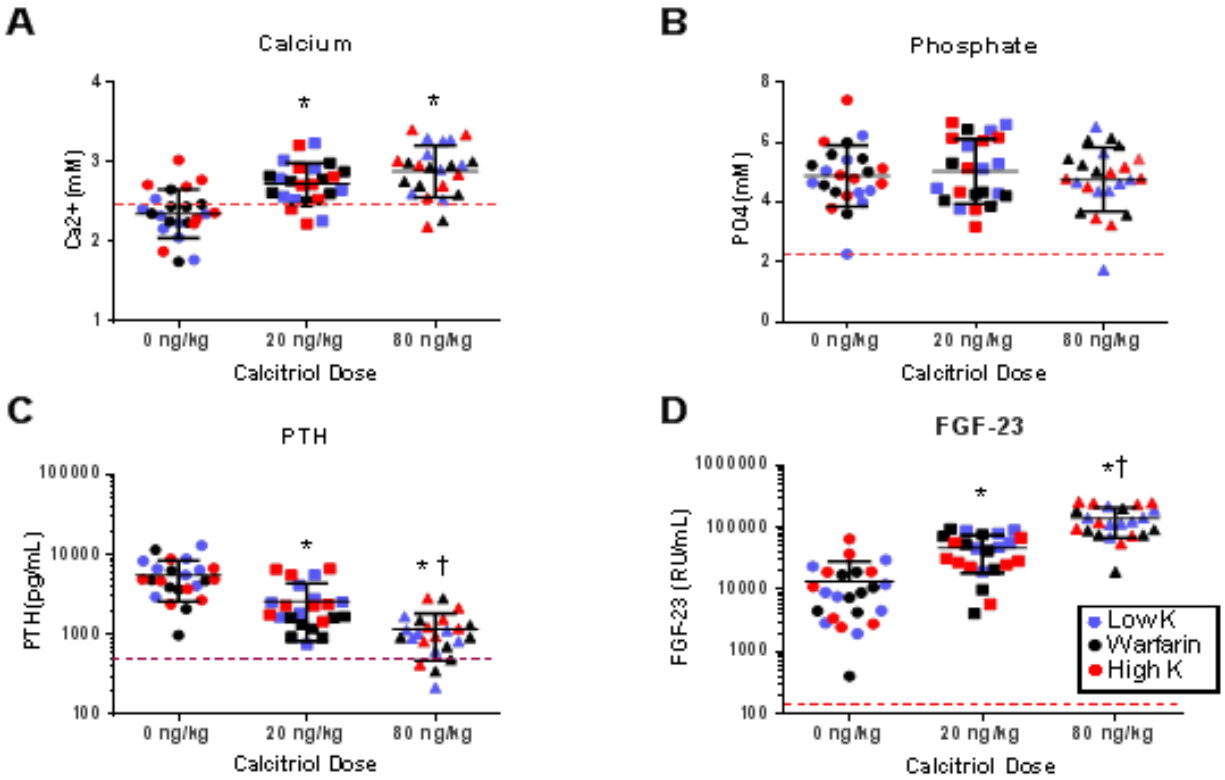
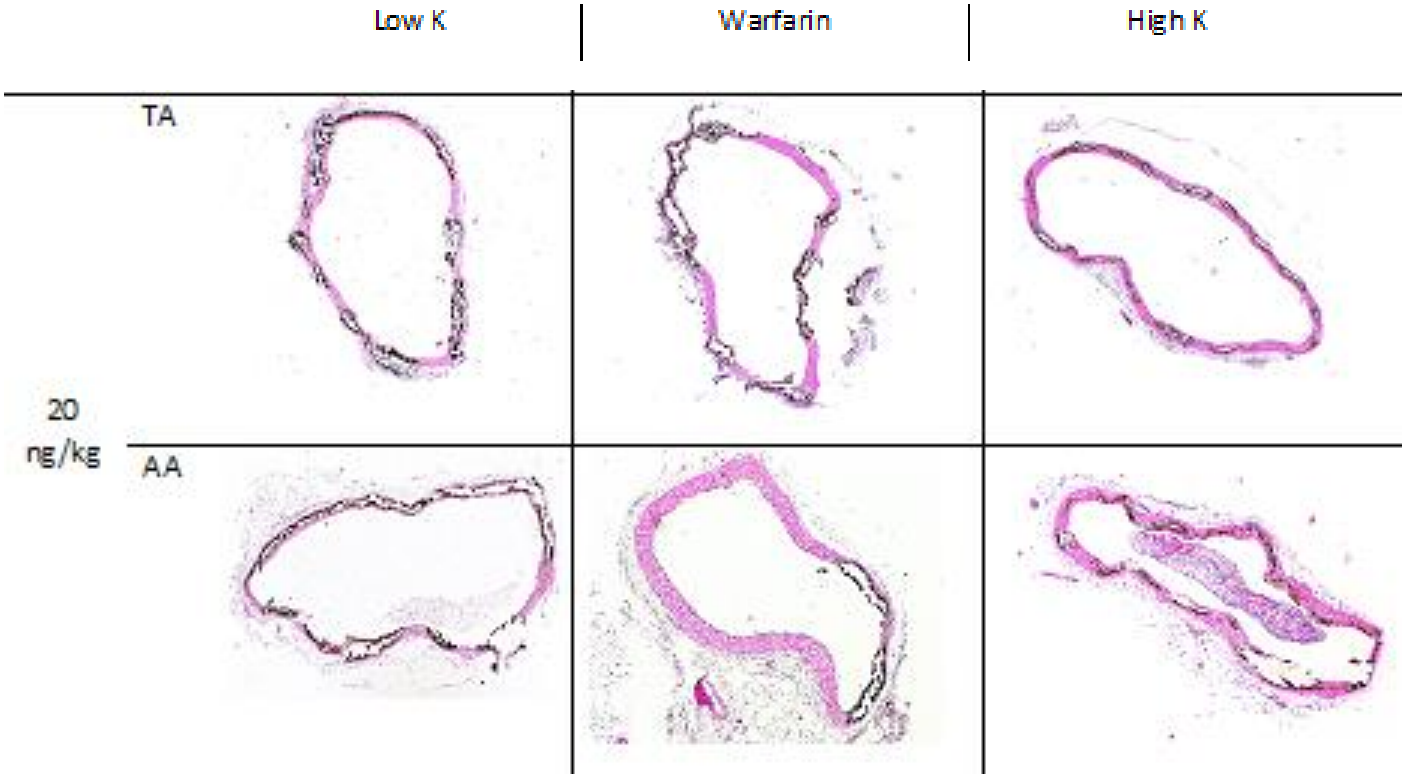


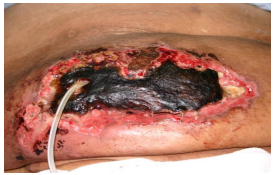
Calcitriol treatment in rats with CKD



CKD rats treated with 20 ng/kg calcitriol daily

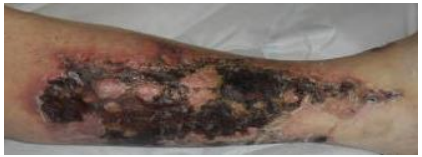
Two cases – triggers

- Patient A – 2004
  - ESKD on PD
  - Poor phosphate control



- Obese
- Insulin injections

- Patient B -2016
  - KT
  - Normal phosphate



- Warfarin
- Calcitriol

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Adapted from **Curr Opin Nephrol Hypertens** 2015, 24:5

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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**

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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

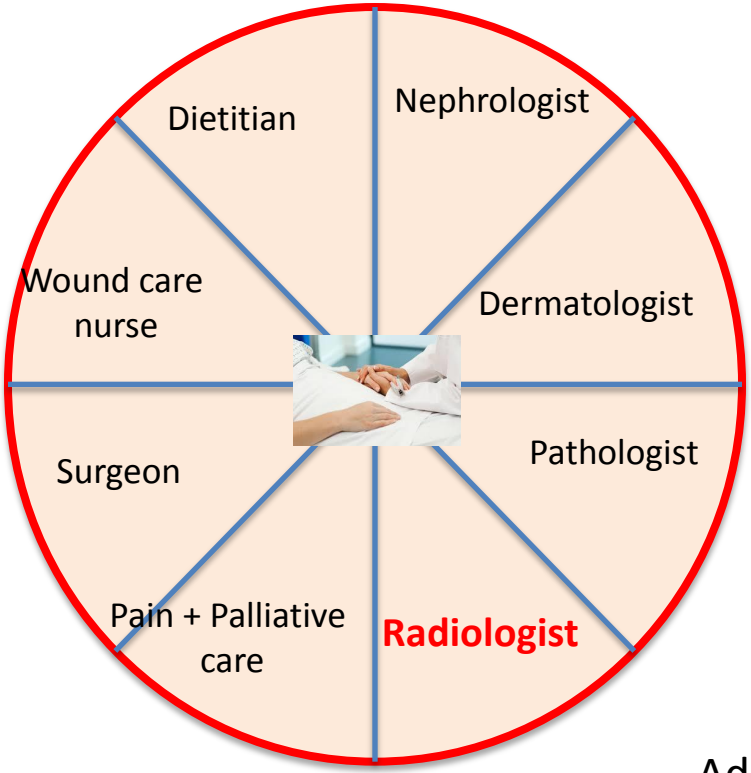
Dermatologist

- 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



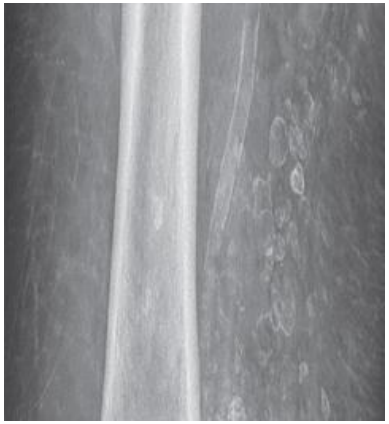
Radiologist

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

Adapted from Curr Opin Nephrol Hyperte

Diagnosis: Imaging studies

- May support the diagnosis when a biopsy is inconclusive or contraindicated



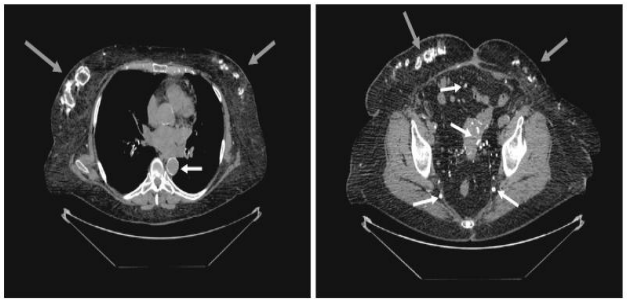
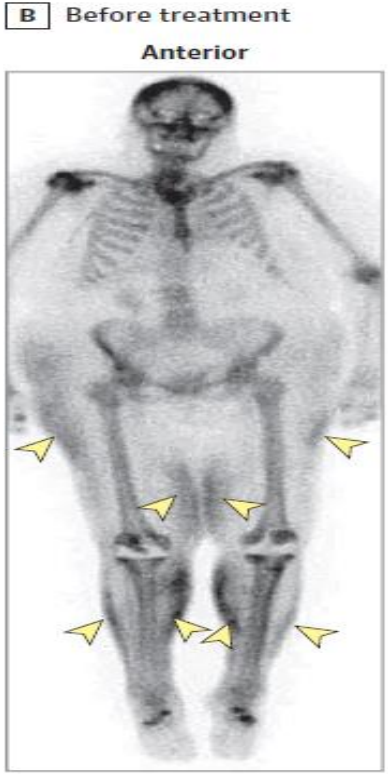
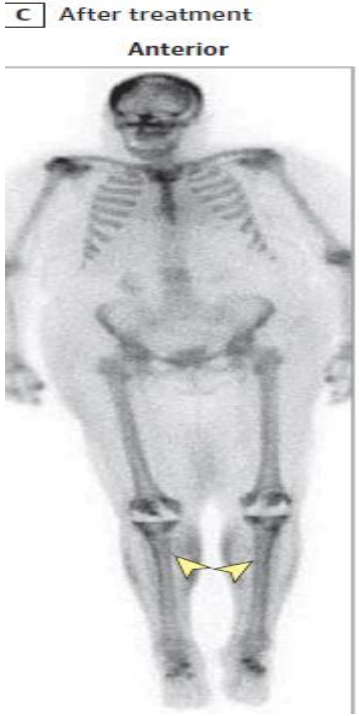


Fig. 1 Extraosseous calcifications detected by CT imaging. *Left*: Unenhanced thoracic computed tomography with severe subcutaneous calcifications of both mammae, pronounced on the right side (*grey arrows*), bronchial calcifications and nearly circular aortosclerosis (*white arrow*). *Right*: Precontrast abdominal computed tomography with disseminated subcutaneous calcifications in the abdominal wall (*grey arrows*) and in smaller pelvic arteries (*white arrows*)

Increased radiotracer uptake in soft tissues on nuclear bone scanning





JAMA Dermatology January 2017 Volume 153, Number 1

Pain and Palliative Care

- **Pain medications**
  - Opiates
  - Opiate alternatives
  - Spinal anesthetic agents
- **Goals of care discussions**

Adapted from **Curr Opin Nephrol Hypertens** 2015, 24:5

Surgeon and Wound Care Nurse

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

Adapted from Curr Opin Nephrol Hyperte

Original Article

Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review

JENNIFER AN,[1] BRIDGET DEVANEY,[2] KHAI YANG OOI,[1] SHARON FORD,[1] GEOFF FRAWLEY[2] and SOLOMON MENAHEM[1]

- 46 patients
- 44 sessions over 2 months led to complete healing in half the patients with peripheral disease

Nephrology **20** (2015) 444–450

BCKD18 BC KIDNEY DAYS

Table 3 Prior studies of the influence of hyperbaric oxygen therapy (HBOT) on calciphylaxis

Author	Year	Cohort	No. of HBOT treatments (range)	Other interventions	Outcome
Podymow *et al*.[15]	2001	5	25–35	Nil	60% improved 40% healed
Basile[20]	2002	11	20–108	PTHX	89% improved 73% healed
Dwyer *et al*.[21]	2002	1	23	Not reported	100% healed
Edsell *et al*.[22]	2008	20	17–83	PTHX	55% improved 30% healed
Rogers *et al*.[23]	2008	12	7–41	Not reported	92% healed
Arenas *et al*.[24]	2008	2	20–30	Cinacalcet, STS, PTHX, sevelamer	100% improved
Alikadic *et al*.[25]	2009	1	19	Iloprost infusion	100% healed
Baldwin *et al*.[26]	2011	7	10–65 HBOT in 6 pts only	Cinacalcet, sevelamer, STS	86% healed
New *et al*.[27]	2011	5	25–30 HBOT in 2 pts only	Calcitriol, cinacalcet , STS, PTHX, sevelamer	80% healed
Malabu *et al*.[28]	2012	6	Not reported	Cinacalcet, STS, PTHX	50% healed
Savoia *et al*.[29]	2013	4	Not reported HBOT in 3 pts only	Cinacalcet, STS	75% improved

Dietitian

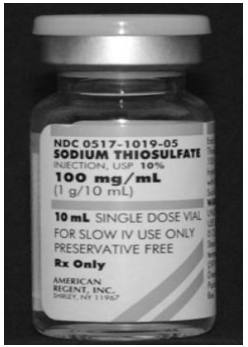
- Dietary phosphate restriction
- Avoiding and treating protein malnutrition

Adapted from Curr Opin Nephrol Hyperte

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

Sandhu et al. Am J Ther. 2012 Jan;19(1):e66-8.
Schlienper et at. Nat Rev Nephrol 2009;5(9): 539–43.

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.

Sandhu et al. Am J Ther. 2012 Jan;19(1):e66-8.
Schlienper et at. Nat Rev Nephrol 2009;5(9): 539–43.

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

www.cjasn.org Vol 8 July, 2013

Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy

Sagar U. Nigwekar,[*†] Steven M. Brunelli,[‡§] Debra Meade,[‖] Weiling Wang,[‖] Jeffrey Hymes,[‖] and Eduardo Lacson Jr.[‖]*

- 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%

www.cjasn.org Vol 8 July, 2013

Table 2. Additional treatment modalities that were undertaken before or during sodium thiosulfate therapy

Treatment Modality	Cases (%)
Initiation/increased dose of non–calcium-based phosphorous binder	59
Initiation of cinacalcet	57
Wound care	34
Discontinuation of vitamin D compounds	30
Increased frequency of hemodialysis sessions	15
Surgical parathyroidectomy	15
Lowering of dialysate calcium	15
Initiation of corticosteroids	9
Switching from nonselective vitamin D analogue to selective analogue	8
Discontinuation of warfarin	6
Discontinuation of calcium-based phosphate binders	4

Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients

- 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

Nephrol Dial Transplant (2013) 28: 1232–1240

Vitamin K

- Some evidence from general population that vitamin K decreases calcification

	VitaVasK	iPACK-HD
Location	Europe	Canada
Patient population	HD patients	HD patients
CAC score criteria	≥ 100 AUs	≥ 30 AUs
Outcome	CAC progression	CAC progression
Drug	K1	K1
Dose	5 mg	10 mg
Frequency	3 times per week	3 times per week
Duration	18 months	12 months

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

Floege et al. Clin J Am Soc Nephrol 10: 800–807, 2015.

CUA – Cinacalcet (EVOLVE)

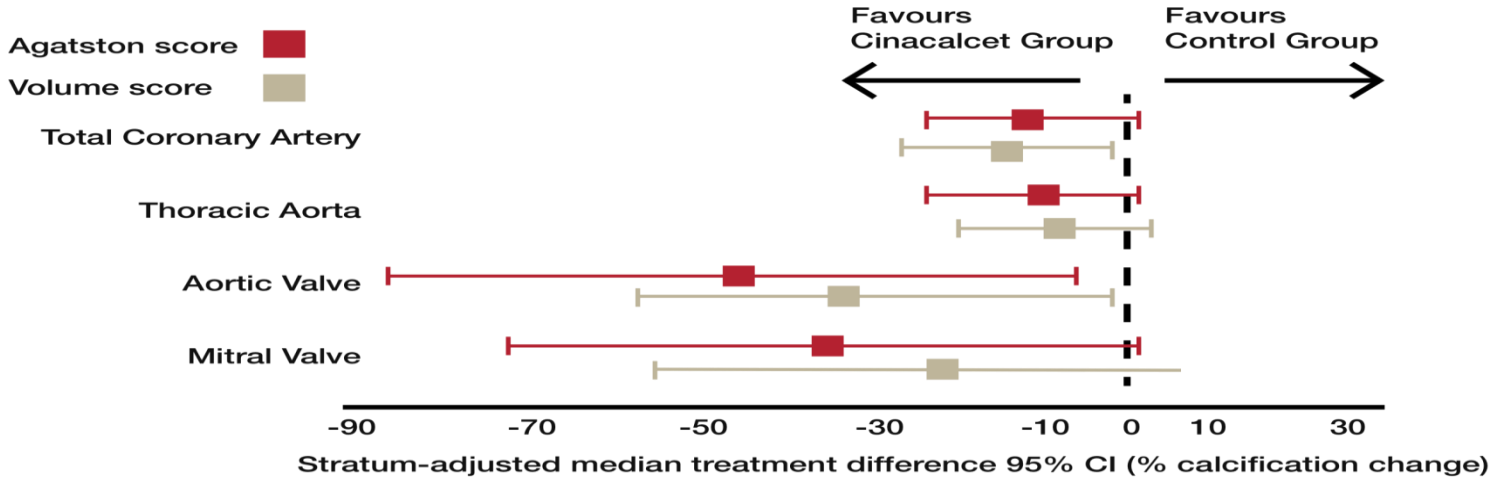
Table 5. Multivariate regression using Fine-Gray subdistributional hazards model of calcific uremic arteriolopathy adverse events (safety analysis set)

Multivariate Model	Hazard Ratio (95% CI)	*P* Value
Treatment (cinacalcet versus placebo)	0.25 (0.10 to 0.67)	<0.01
Male sex (reference, female)	0.33 (0.14 to 0.75)	<0.01
Body mass index (per kg/m^2)	1.09 (1.05 to 1.13)	<0.001
Diastolic BP (per 10 mmHg)	1.50 (1.19 to 1.90)	<0.001
History of dyslipidemia	2.15 (0.90 to 5.15)	0.09
History of parathyroidectomy	5.79 (1.79 to 18.70)	0.003
Baseline tobacco use (reference, never use)		
Current	1.79 (0.54 to 5.89)	0.34
Former	3.04 (1.19 to 7.74)	0.02

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.

Floege et al. Clin J Am Soc Nephrol 10: 800–807, 2015.

ADVANCE: The first RCT to show that Cinacalcet may attenuate the progression of valvular calcification in SHPT

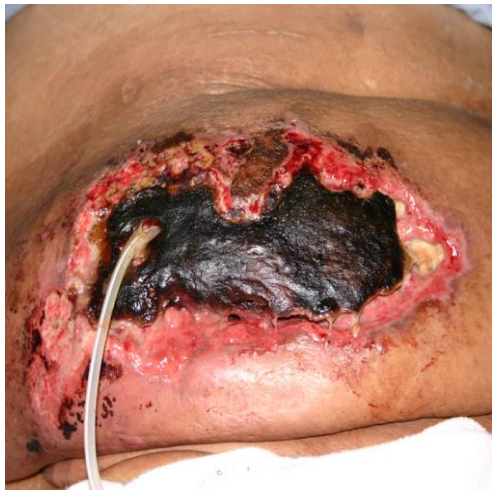


Bisphosphonates

- Pyrophosphate analogues
- Inhibition of osteoclasts
- Prospective series only

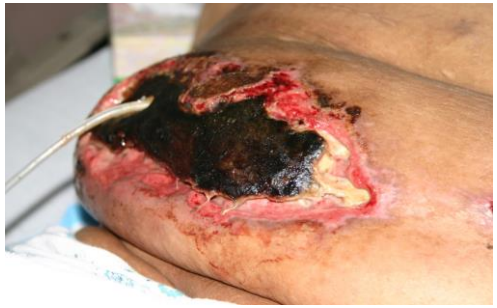
Patient A – central calciphylaxis

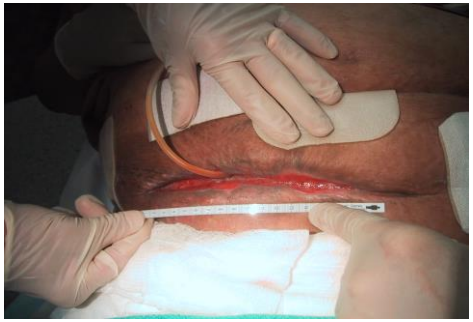
- 42 year old female
- Obese
- ESKD secondary to FSGS
- Type 2 DM on insulin injections
- Peritoneal dialysis
- Presented April, 2004

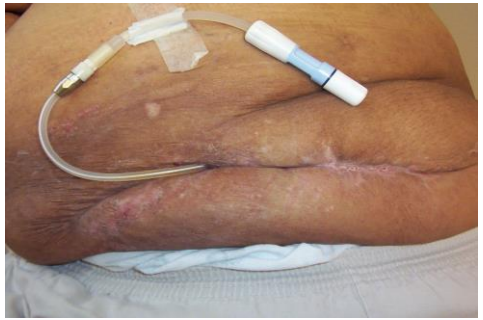


Patient A - 2004

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

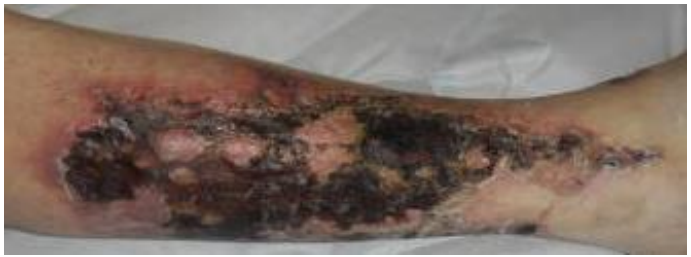






Patient B – 2016

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

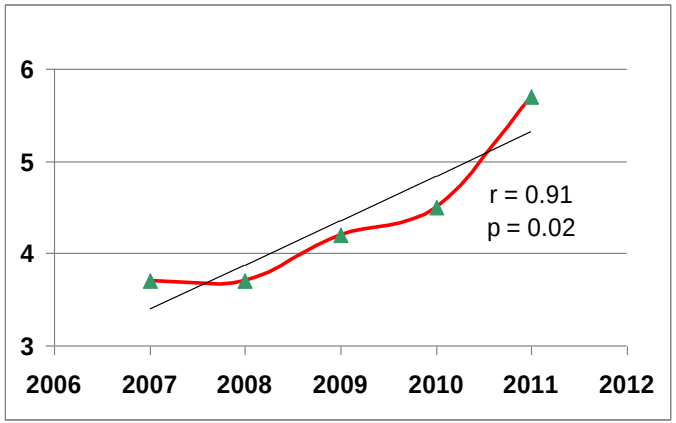


BCKD18
BC KIDNEY DAYS

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

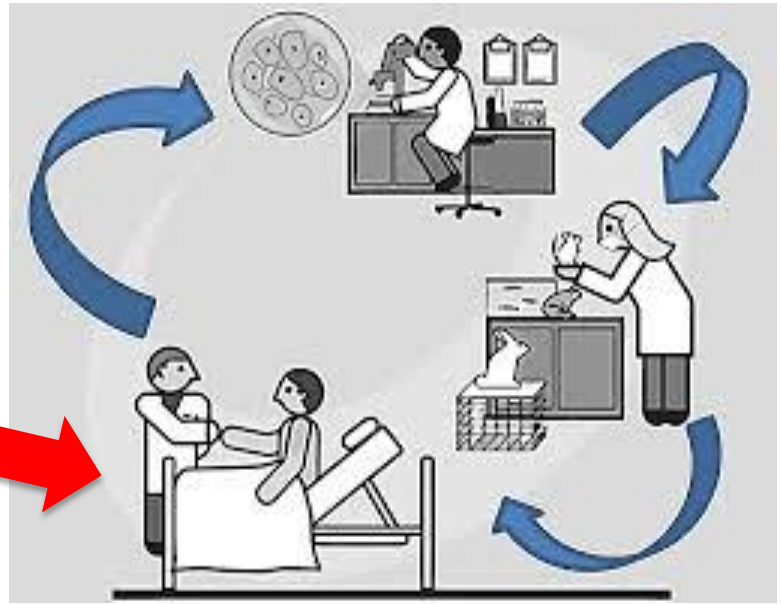
Nigwekar et al. JGIM. 2014;29 (3):724-731

BCKD18 BC KIDNEY DAYS

What is the answer?

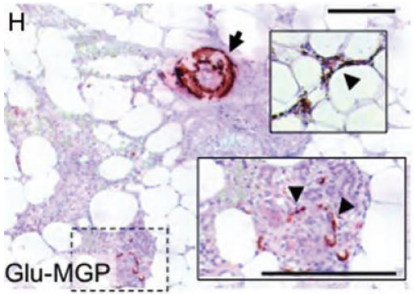
Clinical observations

- VK antagonism



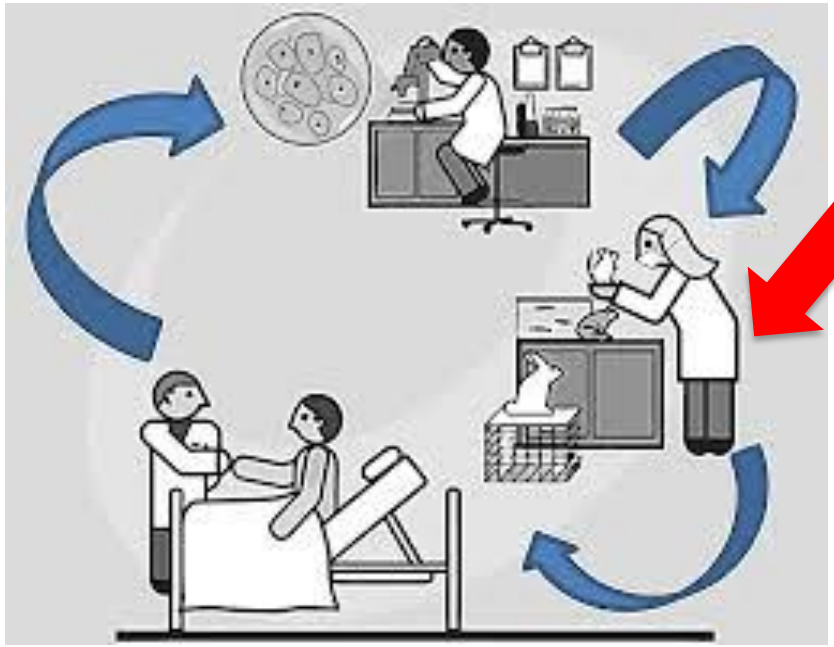
Translational Medicine

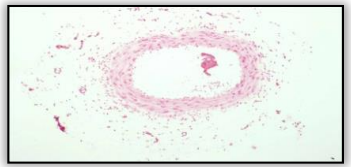
What is the answer?



Translational Medicine

What is the answer?

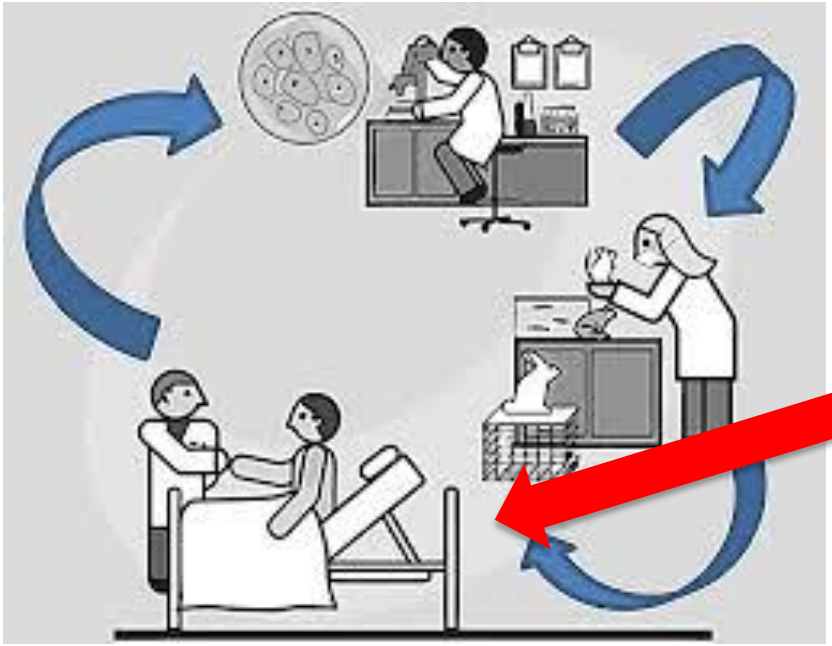




High K diet

Translational Medicine

What is the answer?



VitK-CUA trial

Translational Medicine

Improving the evidence: RCT of Vitamin K

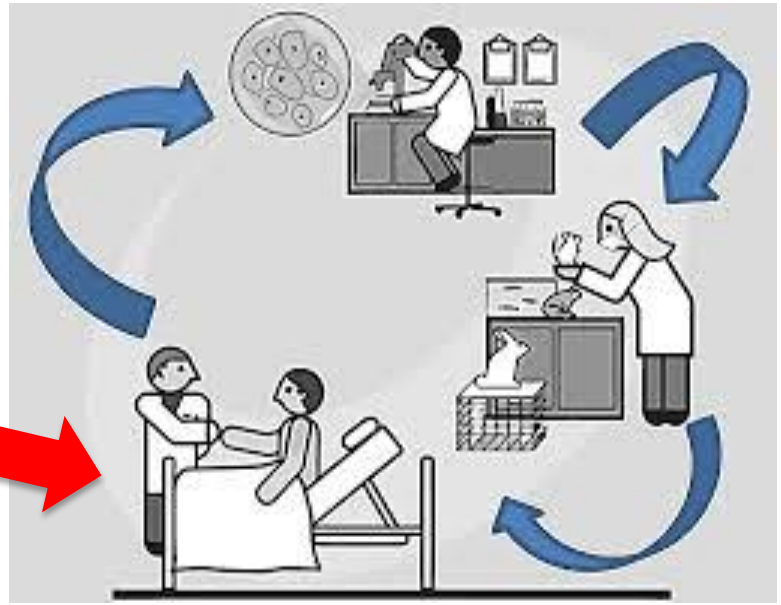
VitK-CUA	Clinicaltrials.gov number, NCT02278692	Phase 2, clinical trial	Massachusetts General Hospital	Single-center, randomized, double-blind, placebo-controlled clinical trial to evaluate the biological efficacy and safety of phytonadione (vitamin K1) in hemodialysis patients with calciphylaxis

- Study eligibility: adult HD patients with calciphylaxis
- Study intervention: vitamin K1 10 mg three times/week for 12 weeks
- Outcomes: pain, skin lesions

What is the answer?

Clinical observations

- CKD-MBD parameters
- CKD-MBD treatments
- Obesity
- Trauma



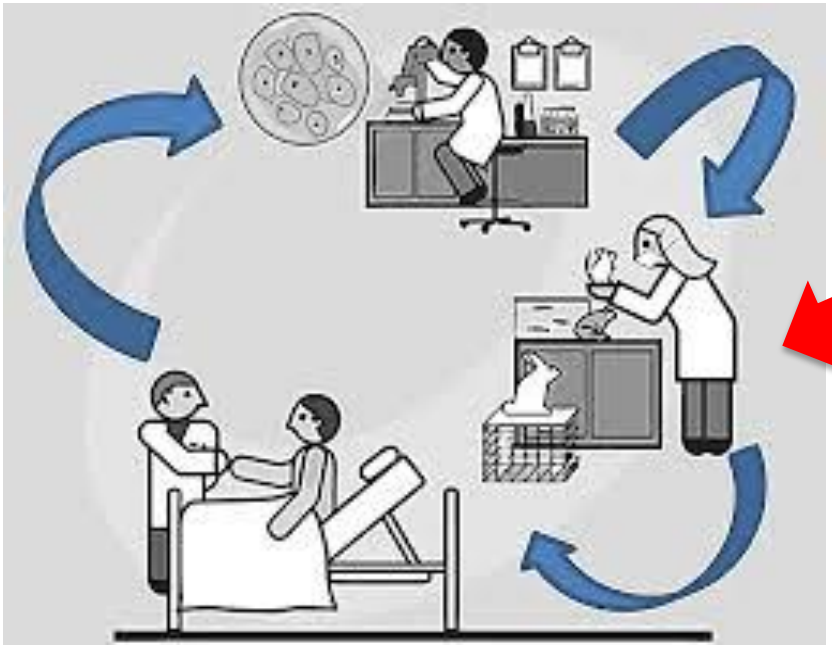
Translational Medicine

What is the answer?

Osteogenic program
'Adipocyte calcification'

Translational Medicine

What is the answer?



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Translational Medicine

Improving the evidence: Active registries

EuCalNet Registry	Prospective registry	RWTH Aachen University	Observational, prospective, non-interventional collection of data and samples from patients with uremic and non-uremic calciphylaxis
Partners Calciphylaxis Biobank	Prospective registry	Massachusetts General Hospital	Observational, prospective, non-interventional collection of data and samples from patients with uremic and non-uremic calciphylaxis
The UK Calciphylaxis Study	Prospective registry	Salford Royal NHS Foundation Trust (UK)	Observational, prospective, non-interventional collection of data and samples from patients with calciphylaxis in the setting of chronic kidney disease

Improving the evidence: Two RCTs of sodium thiosulfate

Study Name	Study ID	Study Type	Sponsor	Comments
A clinical trial with Sodium Thiosulfate for the treatment of Calciphylaxis	ISRCTN number, ISRCTN73380053	Phase 2/3, clinical trial	Dr. F. Köhler Chemie GmbH (Germany)	Multicenter, open-label clinical trial to evaluate the efficacy of intravenous Sodium Thiosulfate for treatment of calciphylaxis wounds in hemodialysis patients
CALISTA Trial	Clinicaltrials.gov number, NCT03150420	Phase 3, clinical trial	Hope Pharmaceuticals	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

The way forward

Table 7. Recorded therapeutic strategies in 165 CUA dialysis patients (76% of the entire dialysis CUA cohort) [multiple answers possible; single answers in $n = 16$ (10%) cases]

Intensifying dialysis therapy	
Increase of dialysis duration and/or frequency	16.9%
Switch from haemodialysis to haemodiafiltration	0.8%
Switch from PD to HD	1.5%
Reduction	
Lowerin	23.8%
Lowerin	1.5%
Reductic	16.2%
including	
Vitamin K	
Stop VK	25.4%
Give vit	17.7%
Secondary	
Initiate	10.8%
Stop cin	2.3%
Parathy	2.3%
Initiate	2.3%
Calcificatic	
Apply S	21.5%
Give bis	2.3%
Fresh fr	1.7%
Tissue oxy	
Revascu	3.8%
Antibiotics	16.1%
Surgical wound management	
Including necrosectomy, debridement and skin transplantation	29.2%
Others	
Application of glucocorticoids	3.1%
Prostaglandin infusion	0.7%

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BC KIDNEY DAYS

Thank you

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