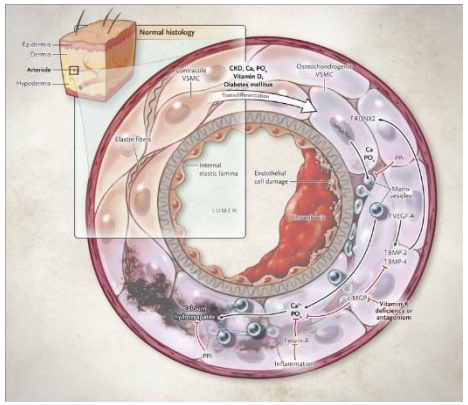
Calcific Uremic Arteriolopathy



Mojgan Mortazavi

Professor of nephrology

Isfahan kidney diseases research center

Isfahan university of medical sciences

CALCIFIC UREMIC ARTERIOLOPATHY (CUA),

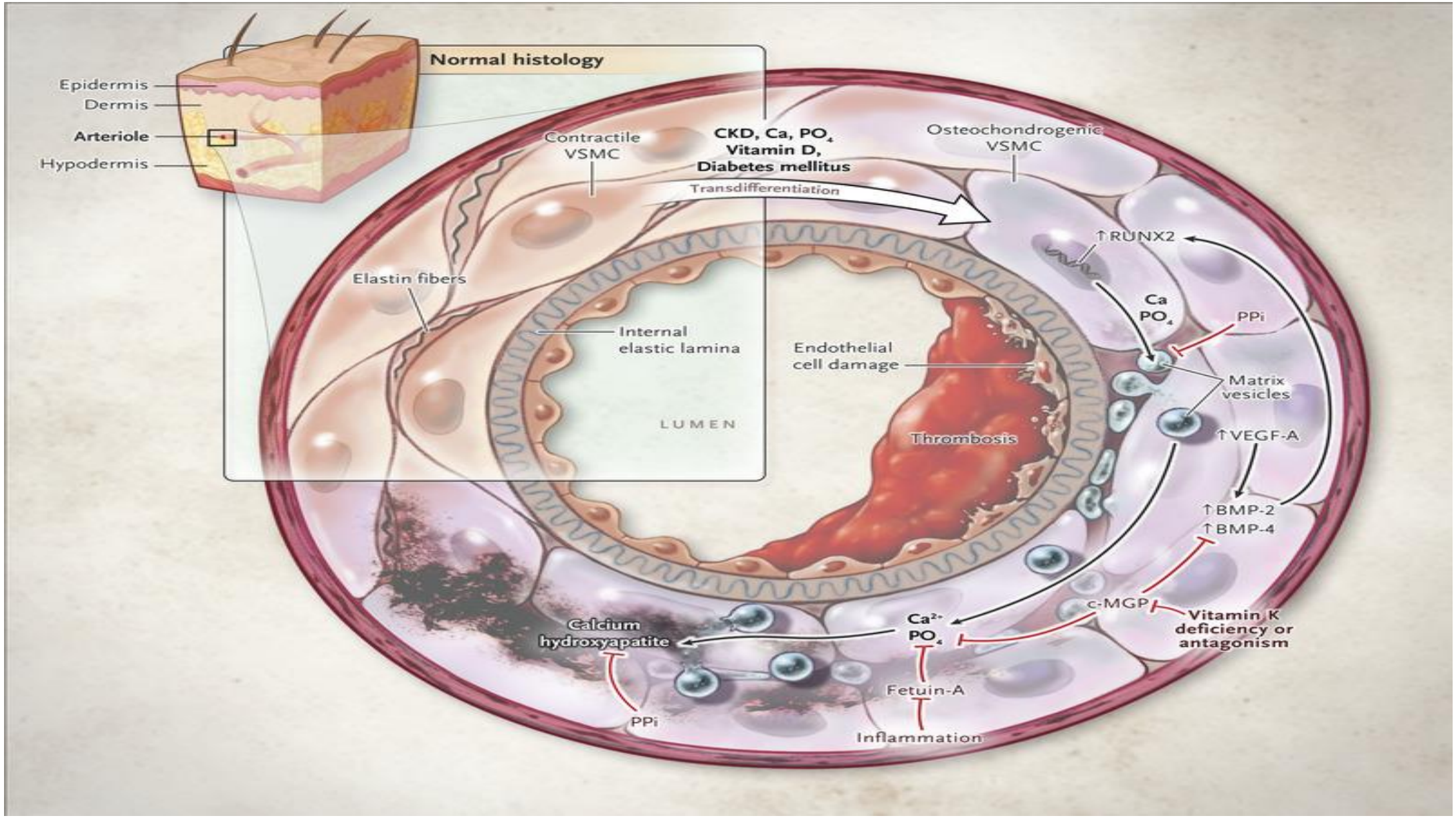
- previously known as “calciphylaxis,” is an unusual disorder seen predominately in dialysis patients and is a thrombotic disorder of skin and subcutaneous tissue
- Early signs and symptoms include livedo reticularis and extremely painful red nodules, which progress to ulcerative and necrotic lesions.
- Risk factors include female gender, obesity, and Caucasian race
- Exposure to the uremic milieu may be responsible for altering vascular smooth muscle cells and increasing the expression of factors involved in ectopic mineralization, such as osteopontin and core-binding factor alpha.

introduction

- Calcific uremic arteriolopathy (CUA) is an often fatal condition with no effective treatment.
- CUA typically presents with painful purpuric plaques and nodules that progress to necrotic ulcers that frequently become superinfected
- CUA has a dismal prognosis, with 1-year mortality between 45% and 80% , and a significant morbidity burden
- The exact pathobiology of CUA remains obscure, and there is no effective treatment.

CALCIFIC UREMIC ARTERIOLOPATHY

- Further mineralization from elevated calcium and phosphorus levels ultimately results in arteriolar calcification, occlusion, and tissue ischemia.


Normal histology
Epidermis
Dermis
Arteriole
Hypodermis
Contractile VSMC
CKD, Ca, PO4
Vitamin D,
Diabetes mellitus
Transdifferentiation
Osteochondrogenic VSMC
↑RUNX2
Elastin fibers
Internal elastic lamina
LUMEN
Endothelial cell damage
Thrombosis
Ca
PO4
PPi
Matrix vesicles
↑VEGF-A
↑BMP-2
↑BMP-4
c-MGP
Vitamin K deficiency or antagonism
Ca2+
PO4
Calcium hydroxyapatite
Fetuin-A
PPi
Inflammation

A high index of suspicion
is necessary to identify the disease as
early as possible

Risk factors

- Accurate identification of risk factors for calcific uremic arteriolopathy (CUA) is necessary to develop preventive strategies for this morbid disease.

Risk factors

- Mortality rates for patients with CUA are extremely high and have remained over three times that for patients receiving hemodialysis without CUA.
- A first step in preventing CUA is to conduct a comprehensive ascertainment of risk factors for CUA.

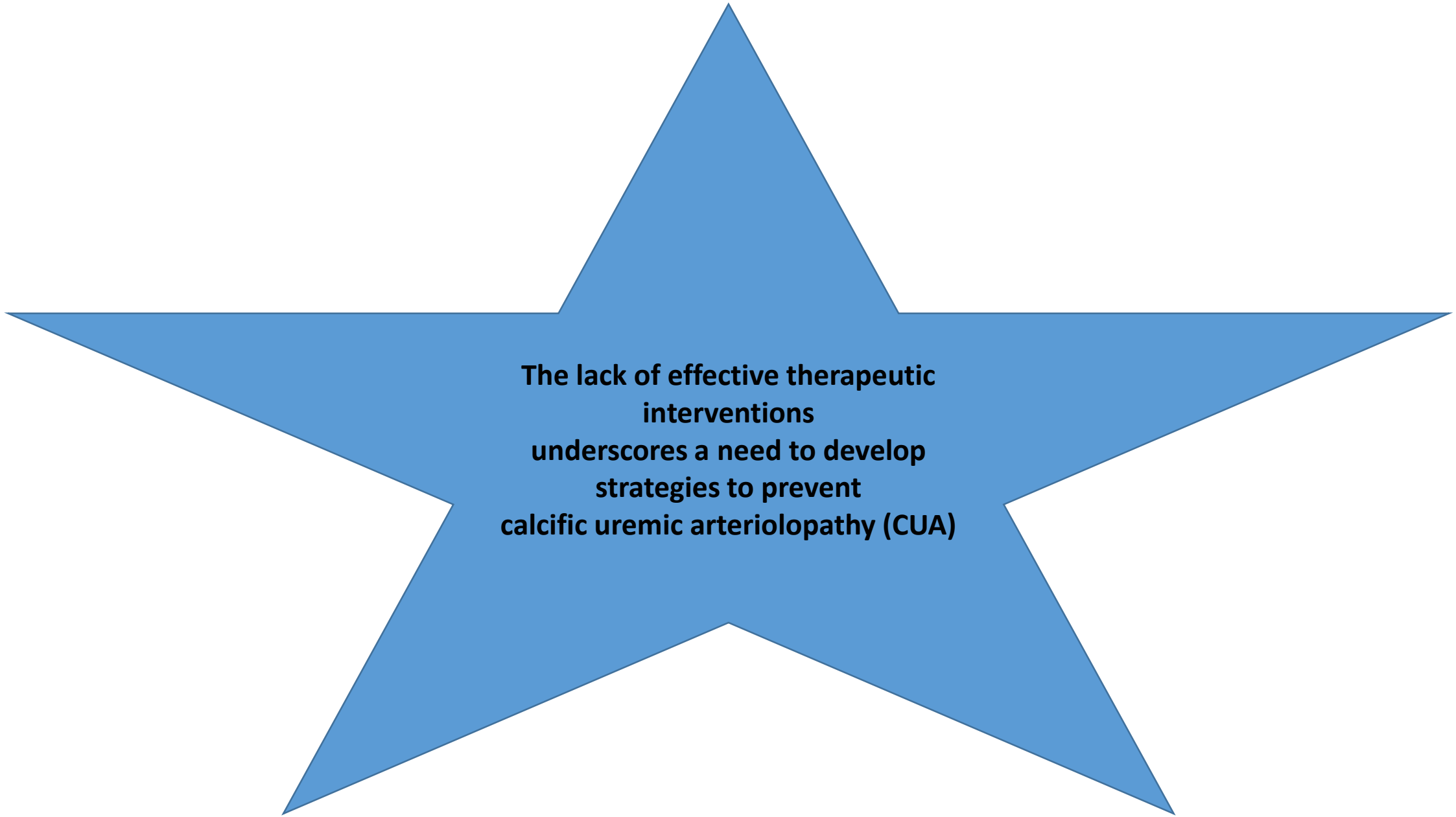
CLINICAL RESEARCH www.jasn.org

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*‡

*Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; †Division of Nephrology, University of North Carolina Kidney Center, Chapel Hill, North Carolina; and ‡Medical office, Fresenius Medical Care North America, Waltham, Massachusetts

J Am Soc Nephrol 27: 3421–3429, 2016. doi: 10.1681/ASN.2015091065


The lack of effective therapeutic interventions
underscores a need to develop strategies to prevent
calcific uremic arteriolopathy (CUA)

trauma are associated with the risk of future CUA.

and controls (Table 1). Mean ages for cases and controls were

Table 1. Comparison of baseline characteristics at hemodialysis initiation between patients who subsequently developed CUA (cases) and age-, sex-, and race-matched patients who did not develop CUA (controls)

Characteristic	Cases (n=1030)	Controls (n=2060)	*P* Value
Demographics			
Age, yr	54±15	55±15	Not applicable
Sex, female %	67	67	Not applicable
Race			Not applicable
White %	49	49	
Black %	28	28	
Other %	23	23	
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
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
Other laboratory parameters and medications			
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

Mean ± SD is reported for all continuous variables except for serum PTH where IQR is reported. ALP, alkaline phosphatase; sPKtV, single pool KtV; ESA, erythropoiesis-stimulating agent; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Table 2. Comparison of baseline characteristics at hemodialysis initiation between patients who subsequently developed central CUA and those who developed peripheral CUA

Characteristic	Central CUA (n=582)	Peripheral CUA (n=128)	P Value
Demographics			
Age, yr	53±14	56±15	0.02
Sex, female %	73	61	0.02
Race			0.26
White, %	57	49	
Black, %	26	32	
Other, %	17	19	
Comorbidities and vital signs			
Diabetes mellitus, %	62	55	0.15
Obesity, %	70	54	0.002
Weight, kg	103.9±27.1	94.7±28.4	0.003
BMI, kg/m^2	37.7±9.9	33.8±9.2	<0.001
Systolic BP, mmHg	149±30	153±35	0.29
Diastolic BP, mmHg	77±17	81±23	0.08
Mineral bone parameters and therapies			
Serum calcium (albumin corrected), mg/dl	9.1±0.8	9.0±0.8	0.47
Serum phosphorus, mg/dl	4.8±2.2	4.8±2.3	0.92
Serum PTH, pg/ml	366 (180, 638)	403 (219, 659)	0.96
Serum ALP, U/L	116.6±83.5	123.2±109.4	0.54
Serum 25-hydroxyvitamin D, ng/ml	18.7±11.3	20.1±11.2	0.25
Dialysate calcium, mmol/L	2.5±0.3	2.5±0.3	0.55
Nutritional vitamin D treatment, %	8	8	0.96
Activated vitamin D treatment, %	36	43	0.14
Cinacalcet treatment, %	6	5	0.63
Phosphate-binding agent treatment, %	37	40	0.63
Other laboratory parameters and medications			
Serum albumin, g/dl	3.5±0.6	3.6±0.6	0.16
Hemoglobin, g/dl	10.4±1.8	10.3±1.6	0.65
Serum bicarbonate, mEq/L	22.0±4.0	22.1±4.2	0.94
sPKtV	1.5±0.5	1.4±0.4	0.51
Warfarin treatment, %	18	8	0.01
Statin treatment, %	26	21	0.34
Erythropoiesis-stimulating agent treatment, %	51	48	0.57
Angiotensin pathway blocker treatment, %	17	14	0.38
Insulin treatment, %	22	14	0.06

Mean ± SD is reported for all continuous variables except for serum PTH where IQR is reported. ALP, alkaline phosphatase; sPKtV, single pool KtV.

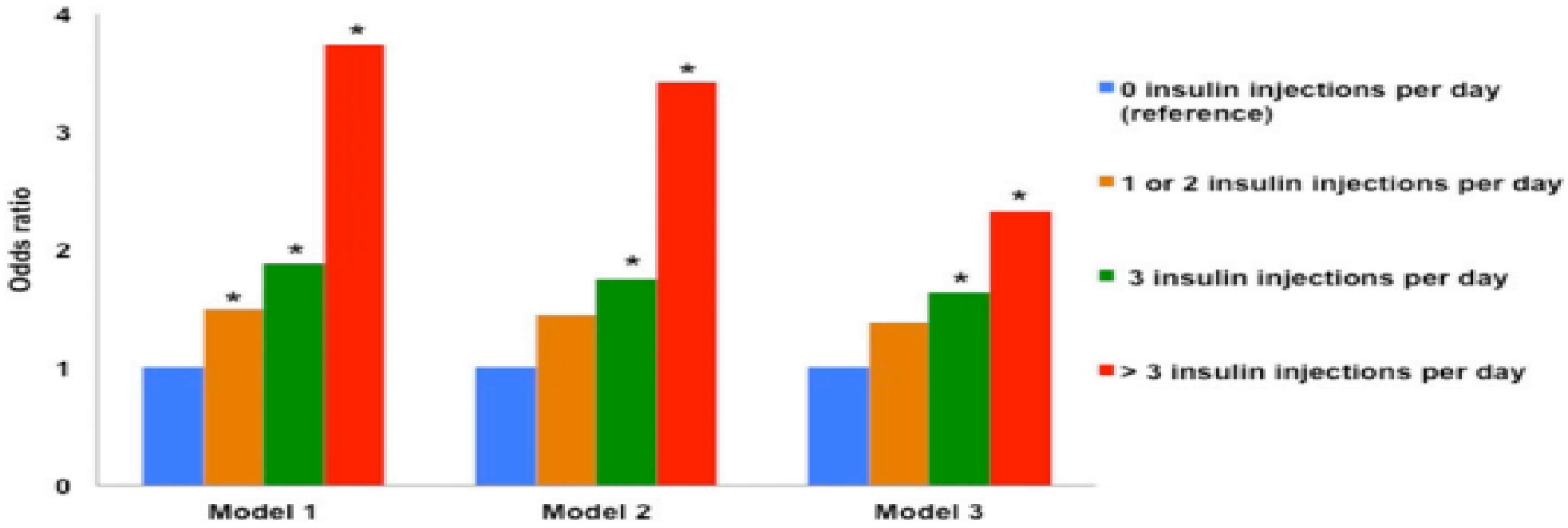


Figure 2. ORs of future CUA involving lower abdomen and/or upper thigh areas by number of insulin injections per day at hemodialysis initiation. Model 1 is an unadjusted model; model 2 is adjusted for age, race, and sex; model 3 is adjusted for covariates independently associated with increased risk of CUA involving lower abdomen and/or upper thigh areas in patients with diabetes mellitus. *$P \leq 0.05$ (significant difference from reference values; zero insulin injections per day).

Result

- Median duration between hemodialysis initiation and subsequent CUA development was 925 days (interquartile range, 273–2185 days
- In multivariable conditional logistic regression analyses, diabetes mellitus; higher body mass index; higher levels of serum calcium, phosphorous, and parathyroid hormone; and nutritional vitamin D, cinacalcet, and warfarin treatments were associated with increased odds of subsequent CUA development
- Compared with patients with diabetes receiving no insulin injections, those receiving insulin injections had a dose response increase in the odds of CUA involving lower abdomen and/or upper thigh areas suggesting a dose-effect relationship between recurrent skin trauma and CUA risk.
- The presence of risk factors months to years before CUA development observed in this study will direct the design of preventive strategies and inform CUA pathobiology

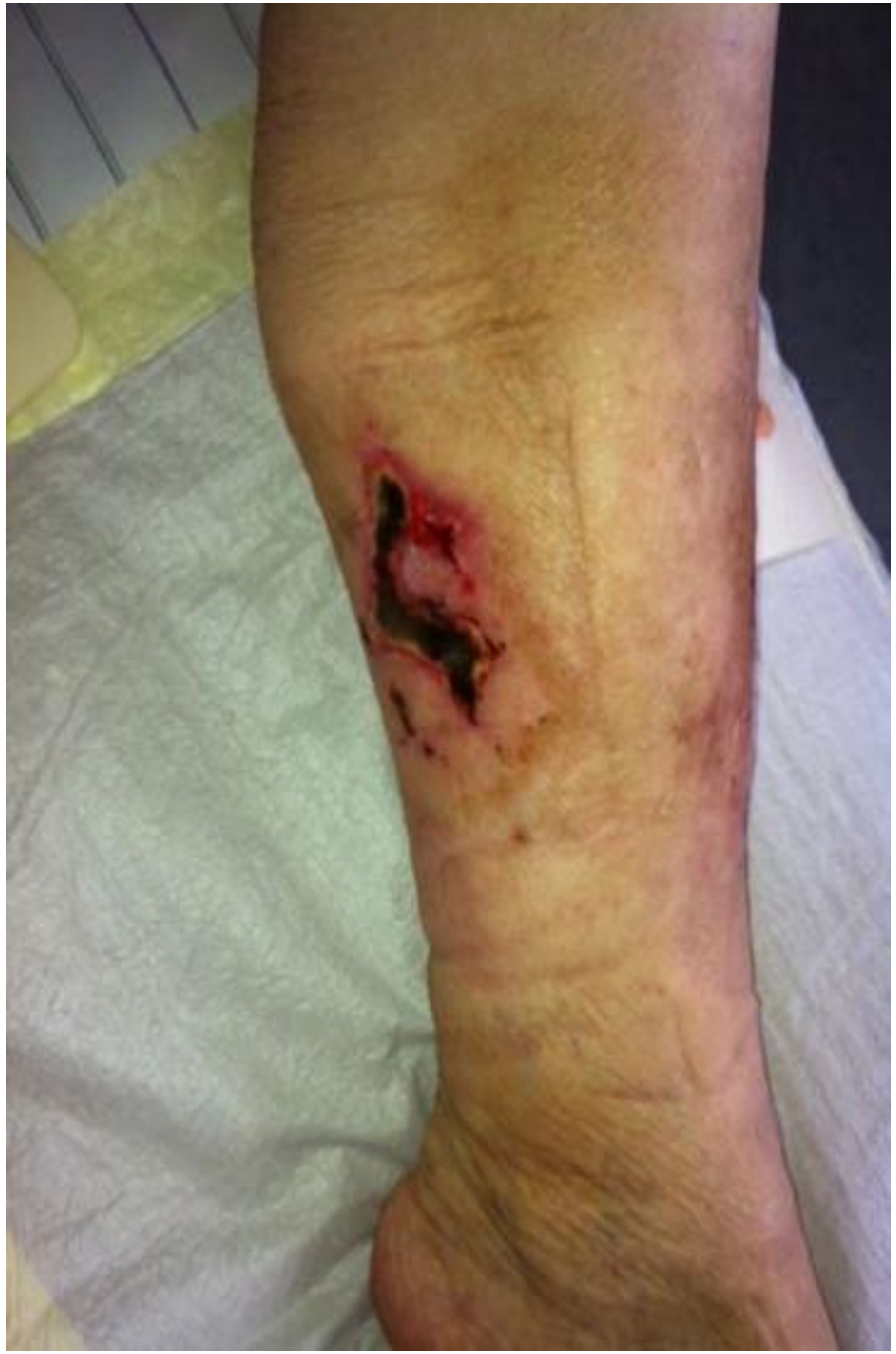
Differential diagnosis

- differential diagnosis includes vasculitis, coumadin-associated skin necrosis, cryoglobulinemia, calcinosis cutis, and panniculitis.

- Bone scan has been reported to identify calcium deposition

in 97% with early plaque-only .

- Skin biopsy shows characteristic arteriolar calcifications in the medial layer.



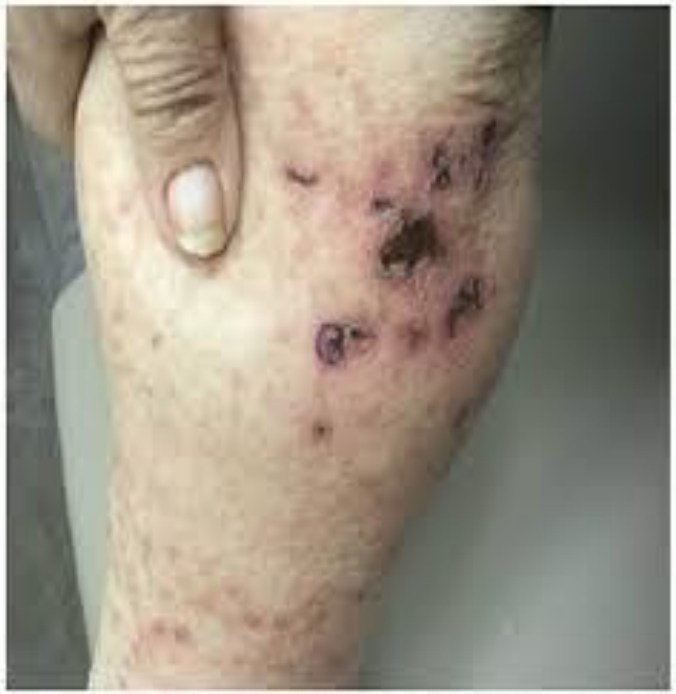
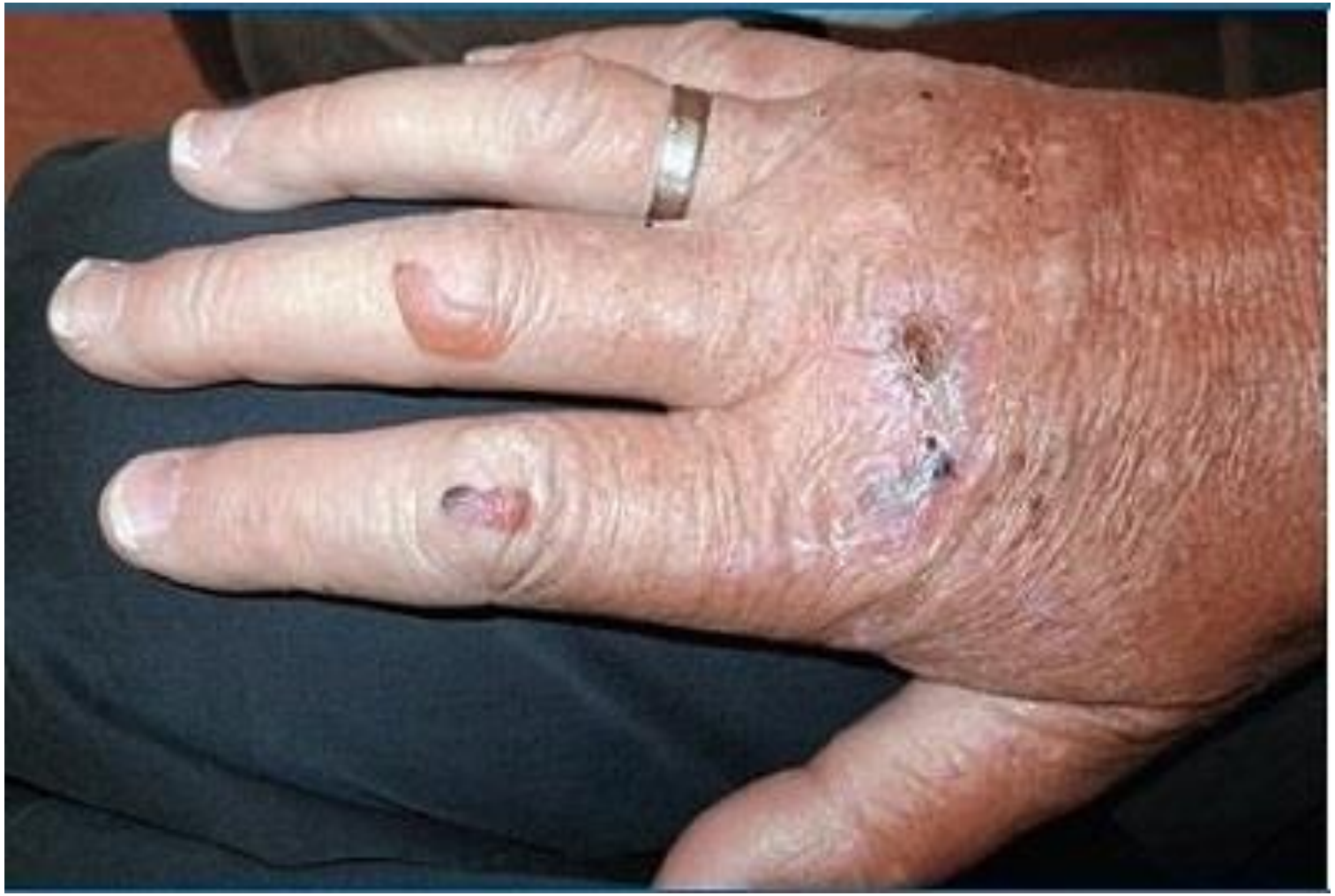
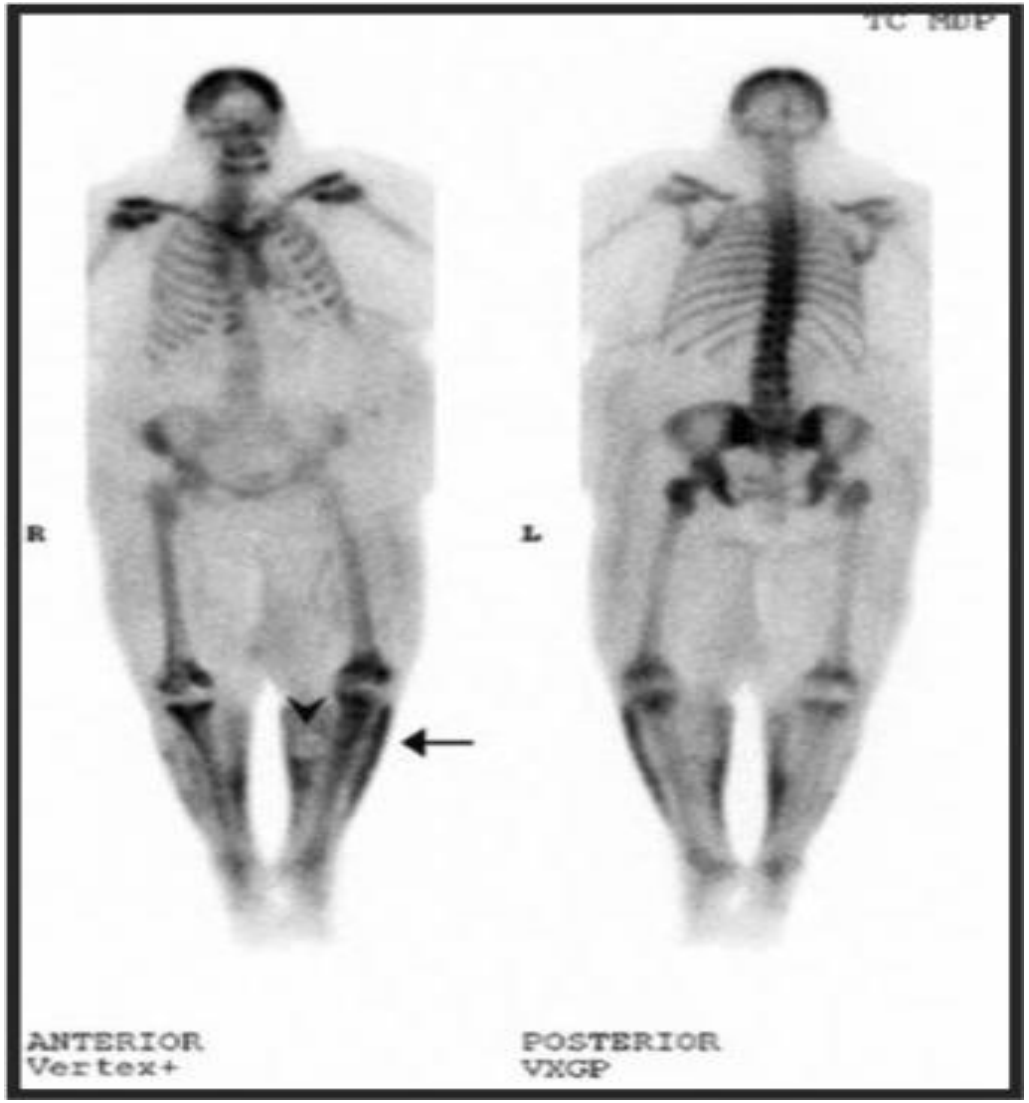


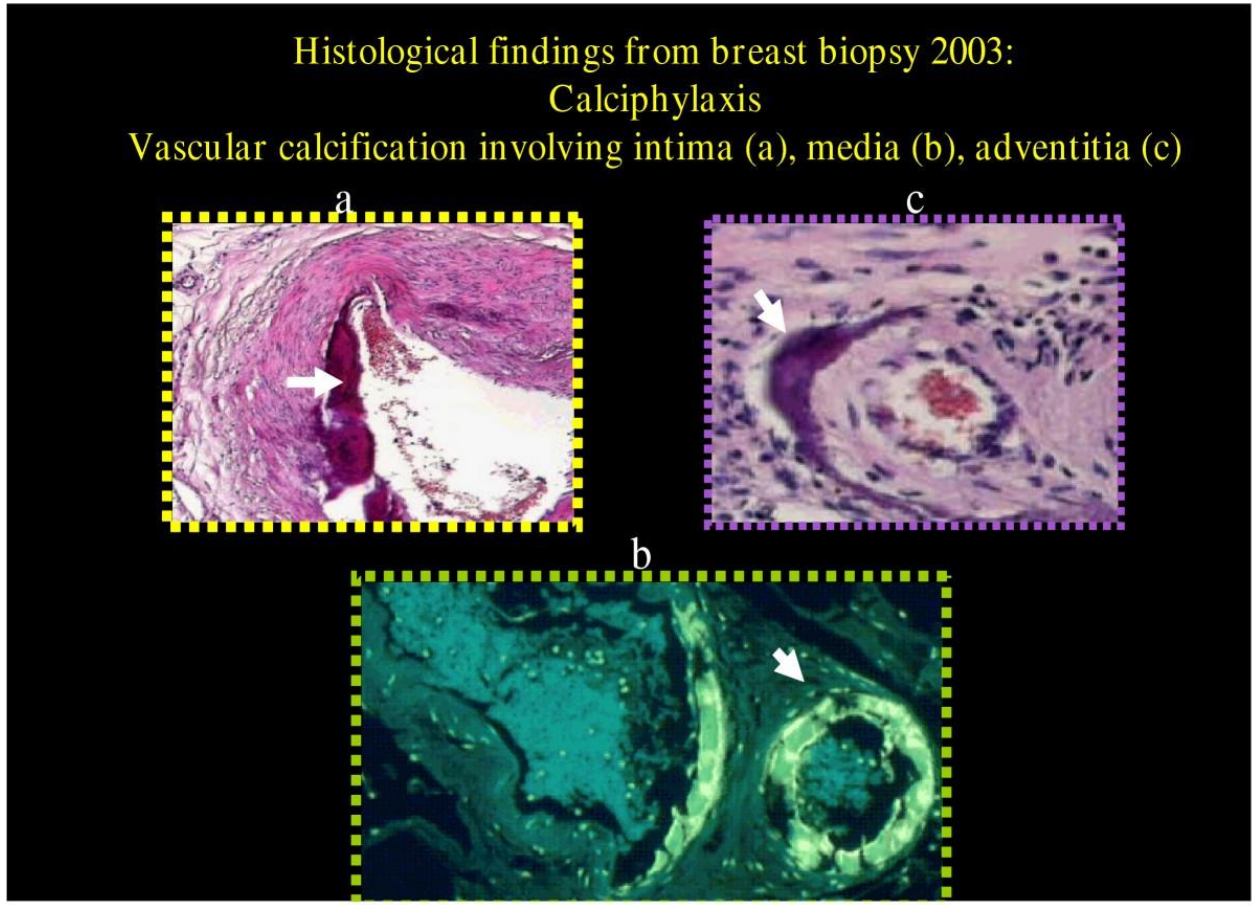
Figure 1. Lesions on the day of biopsy; retiform purpura and hemorrhagic ulcers involving the right calf.



Bone scan

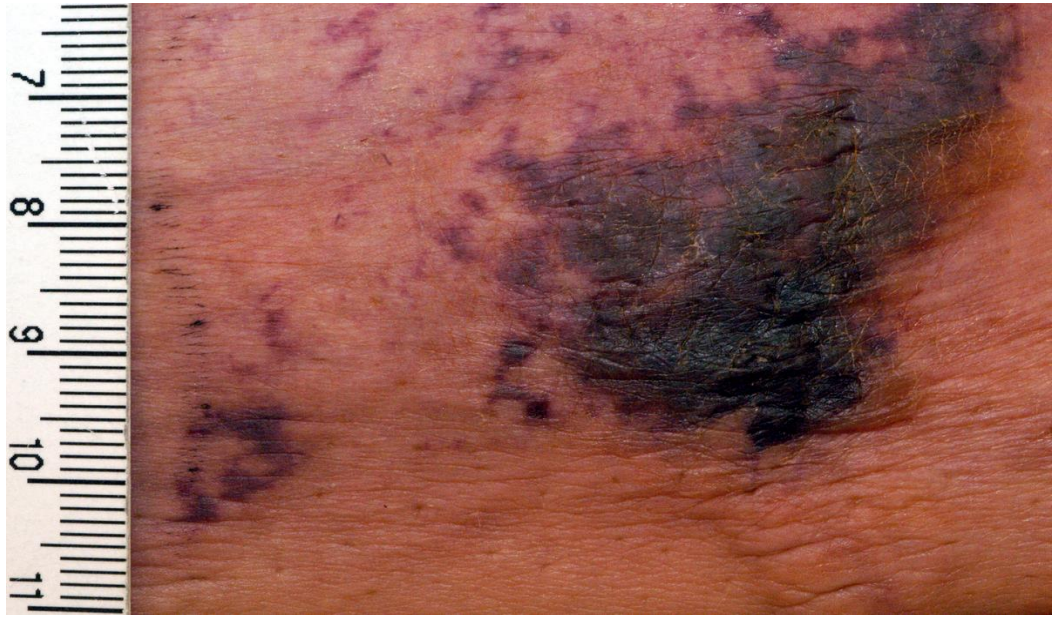


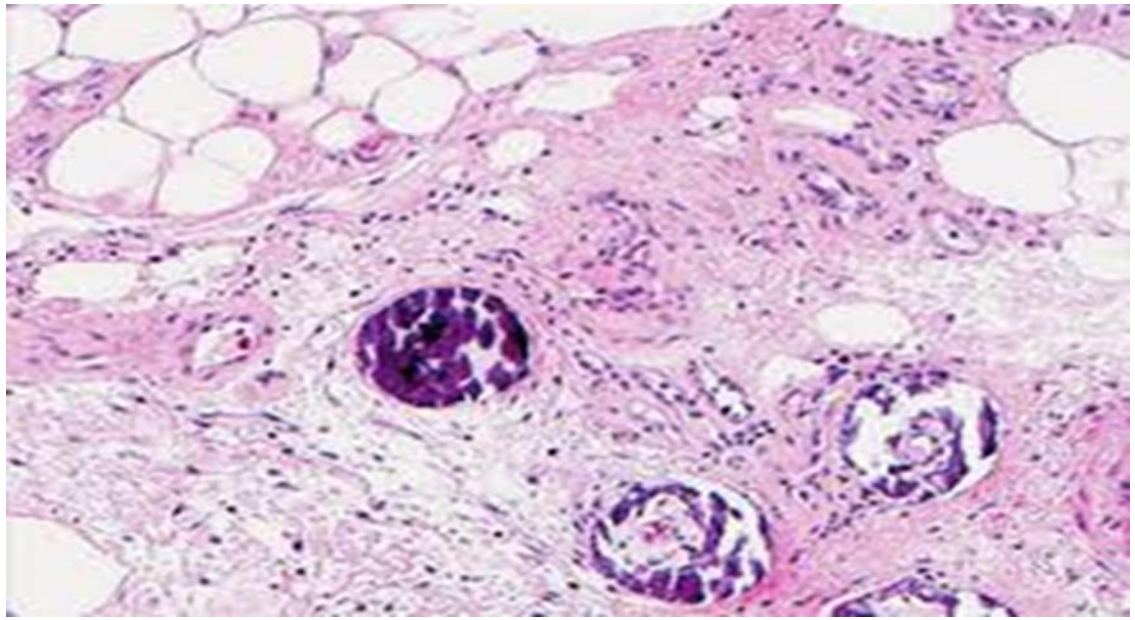
Pathology


Histological findings from breast biopsy 2003:
Calciphylaxis
Vascular calcification involving intima (a), media (b), adventitia (c)
a
c
b

Calciphylaxis
Skin biopsy

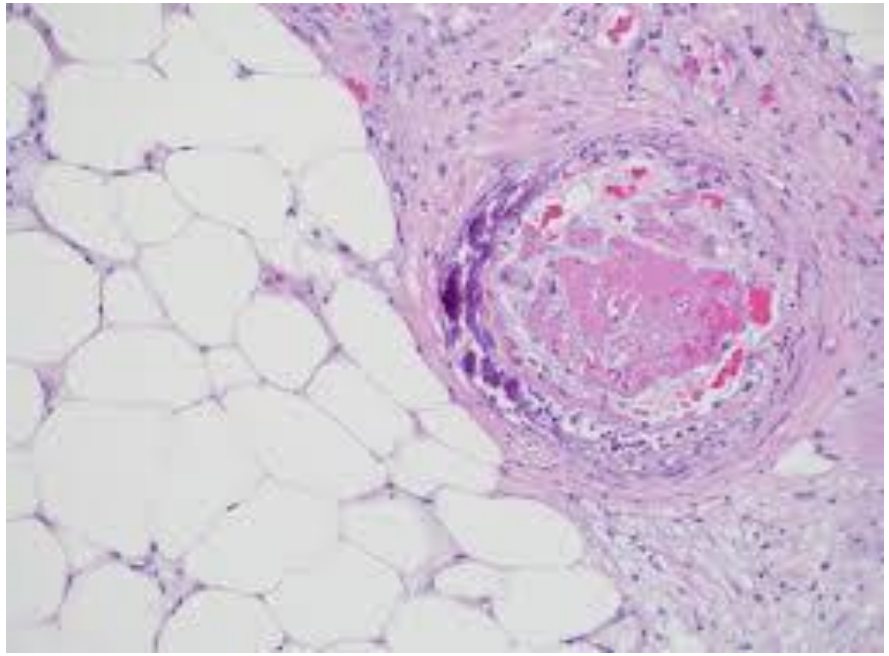
- A deep wedge biopsy is the standard for confirming the diagnosis, as a punch biopsy may be too superficial
- A punch biopsy with a double trephine technique is the preferred biopsy method.14,28 An 8-mm circular core of superficial tissue is first obtained using an 8-mm punch tool. Then, a 4- to 6-mm punch tool is inserted within the center of the 8-mm defect to obtain the deep subcutaneous fat.
- The biopsy should be taken from the margin of the lesion, avoiding the center of the lesion or the necrotic area where nonspecific necrotic tissue is more likely to be found.

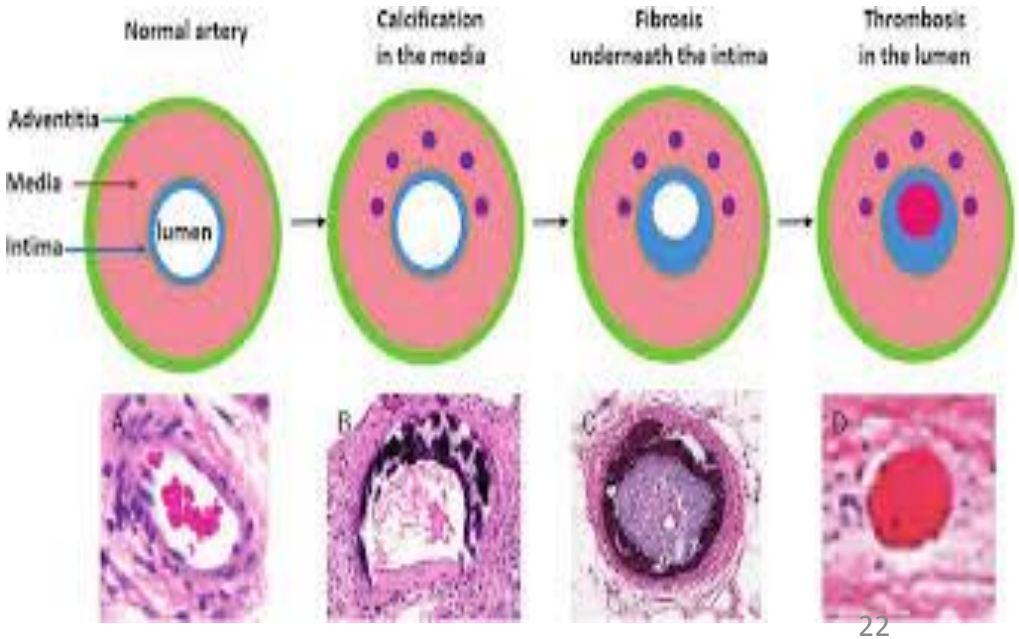




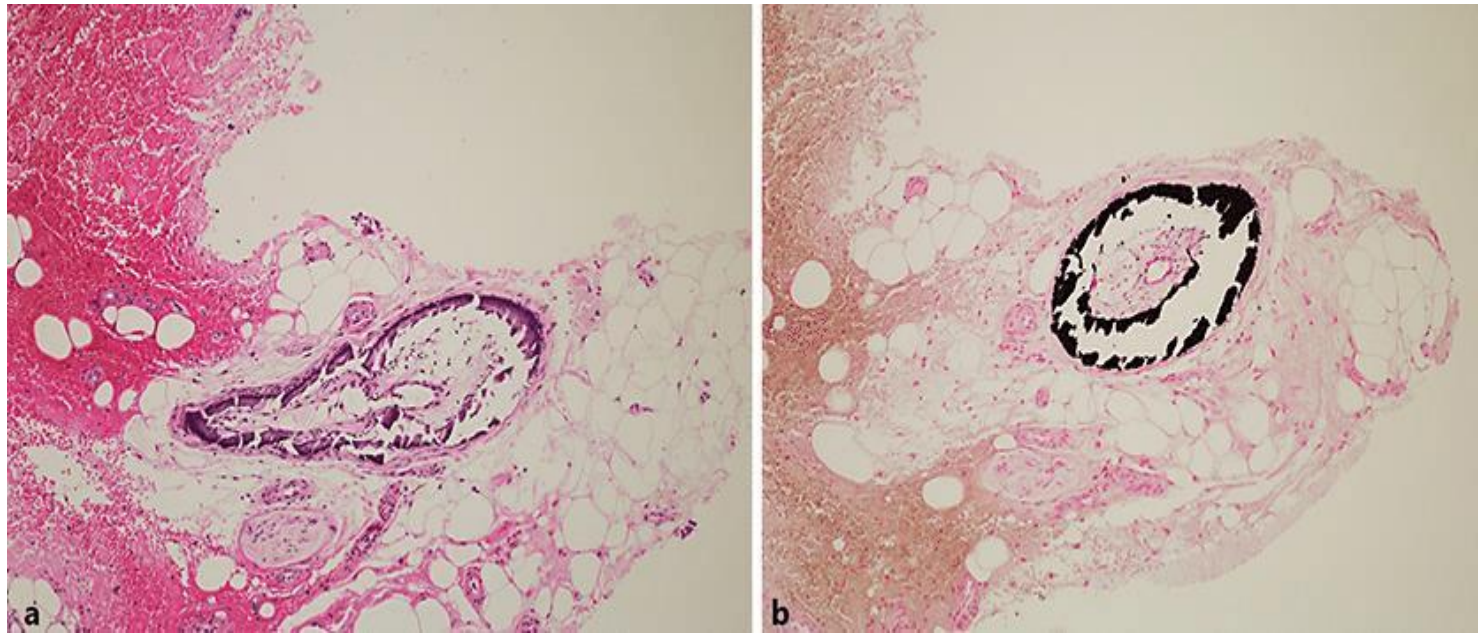
Histopathology of calciphylaxis

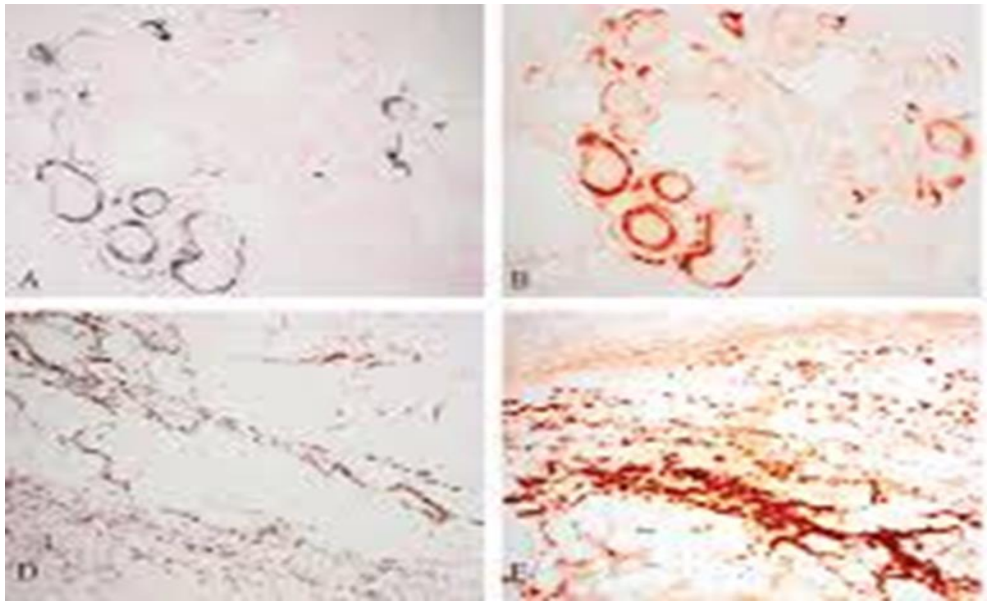
- Calciphylaxis is an occlusive disease of cutaneous blood vessels .Their lumens undergo progressive narrowing first by calcification within the media layer of vessel walls (also known as medial calcification) and proliferation of endothelial cells and fibrosis underneath the intima (also known as subintimal fibroplasia). When thrombosis later develops in the vessel lumen, ischemic injuries develop.Recanalization may subsequently occur.
- It involves the small and medium-sized arterioles in the lower dermis and subcutis. It is often segmental circumferential.
- In well-formed lesions, there is a moderately dense infiltrate composed of neutrophils, lymphocytes, and histiocytes surrounding vessels. There is usually epidermal ulceration and focal dermal necrosis





- Calcium salts are easily recognized in **hematoxylin and eosin** sections by their intense, uniform basophilia.
- if necessary, their nature may be confirmed by **von Kossa's** silver stain which blackens the deposits.
- **Alizarin red S** forms an orange-red lake with calcium at a pH of 4.2. It works best with small amounts of calcium (such as in Michaelis-Gutman bodies





- Twenty-four calciphylaxis patients were identified, with median age of 63.5 years. Seven of 24 (29%) of specimens were inadequate (e.g., lack of subcutaneous adipose tissue for evaluation). Eight of 17 (47%) of adequate specimens had a first false-negative pathologic diagnosis of calciphylaxis.
- Adequate sampling, dermatopathology training, and use of histochemical stains to identify calcium associate with decreased false-negative rate for calciphylaxis diagnosis

Factors associated with false-negative pathologic diagnosis of calciphylaxis, Erik A. Williams Andrea P. Moy Nicole A. Cipriani Sagar U. Nigwekar Rosalynn M. Nazarian, :journal of cutaneous pathology, 02 October 2018


Treatment

Treatment

- Because calcification of arterioles within the dermis is a key

histologic feature of CUA, strategies that target calcification have been suggested; however, their effectiveness has not been confirmed

"Hand book of dialysis 2015"

Treatment

- Once the diagnosis is made, calcium-containing supplements and vitamin D analogs should be discontinued, and non–calcium-based phosphorus-binders should be titrated for aggressive phosphorus control.
- Coumadin, which inhibits the calcium regulatory matrix gla-protein, should be discontinued.

"Hand book of dialysis 2015"

Parathyroidectomy

- Parathyroidectomy is recommended for those with CUA and elevated iPTH (>500 pg/mL (53 pmol/L)), though hyperparathyroidism is not required for CUA, and patients may in fact have low to normal iPTH levels (Bleyer, 1998).

"Hand book of dialysis 2015"

Other treatment

- Pamidronate has also been cited in a single case report to effect rapid clinical improvement (Monney, 2004).
- Wound care is critically important in ulcerative lesions, and surgical debridement and antibiotics may be necessary.
- Hyperbaric oxygen (Basile, 2002) and low-dose tissue plasminogen activator (Sewell & Pittelkow,2004) have been reported to promote wound healing in single case studies.

"Hand book of dialysis 2015"

Sodium thiosulfate

- Sodium thiosulfate, at a dose of 25 g IV three times per week, has been reported to completely resolve the lesions in 26% and improve

the process in 47% (Nigwekar, 2013)

"Hand book of dialysis 2015"

Article

Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy

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

Clin J Am Soc Nephrol 8: 1162–1170, 2013. doi: 10.2215/CJN.09880912

Sodium thiosulfate (STS)

- Cicone et al. first reported that administration of sodium thiosulfate (STS) may be useful in treating CUA.

- This study included 172 patients undergoing maintenance hemodialysis who had CUA and were treated with STS between August 2006 and June 2009 at Fresenius Medical Care North America.
- Of these, 85% completed STS therapy

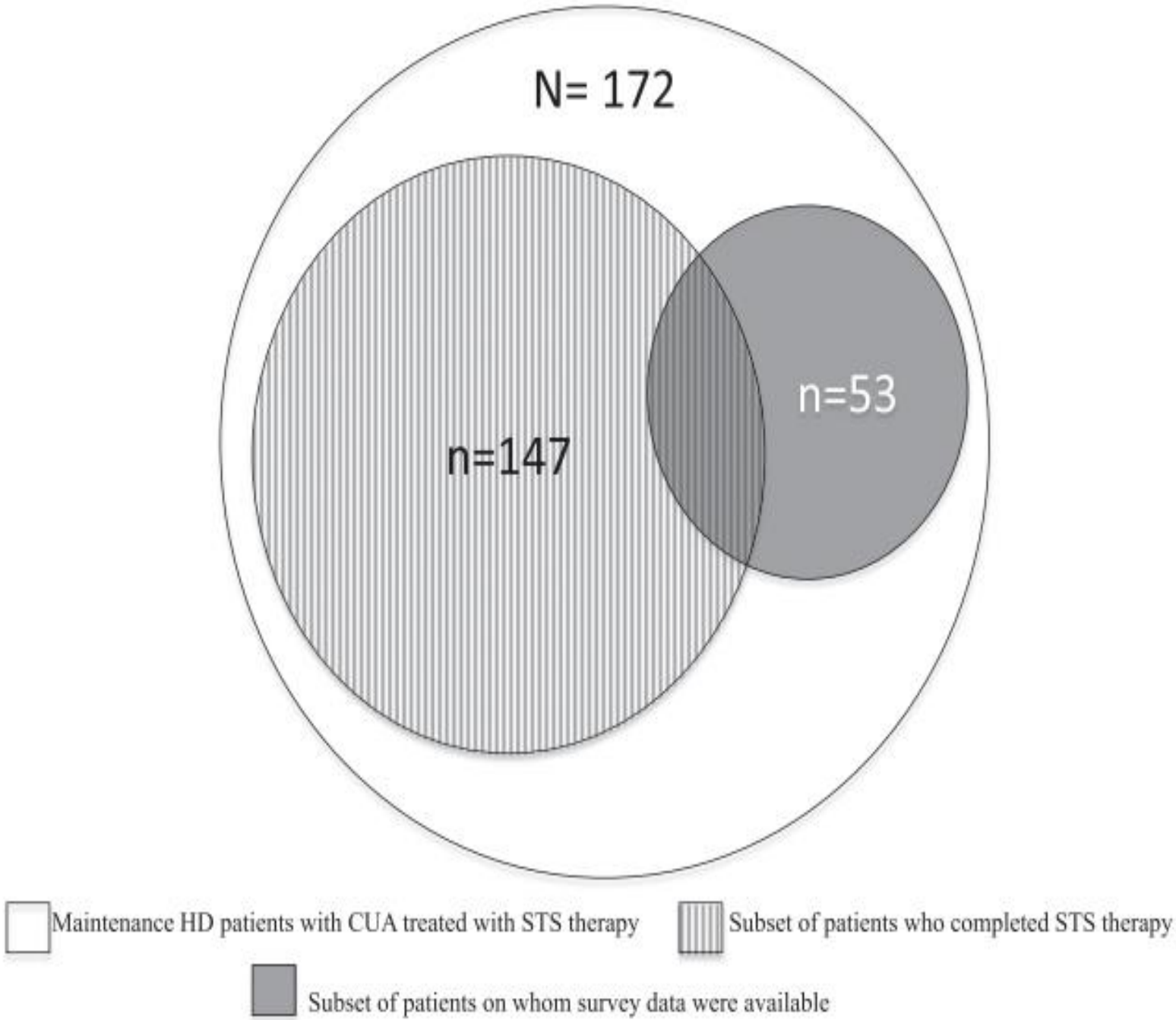

N= 172
n=147
n=53
Maintenance HD patients with CUA treated with STS therapy
Subset of patients who completed STS therapy
Subset of patients on whom survey data were available

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

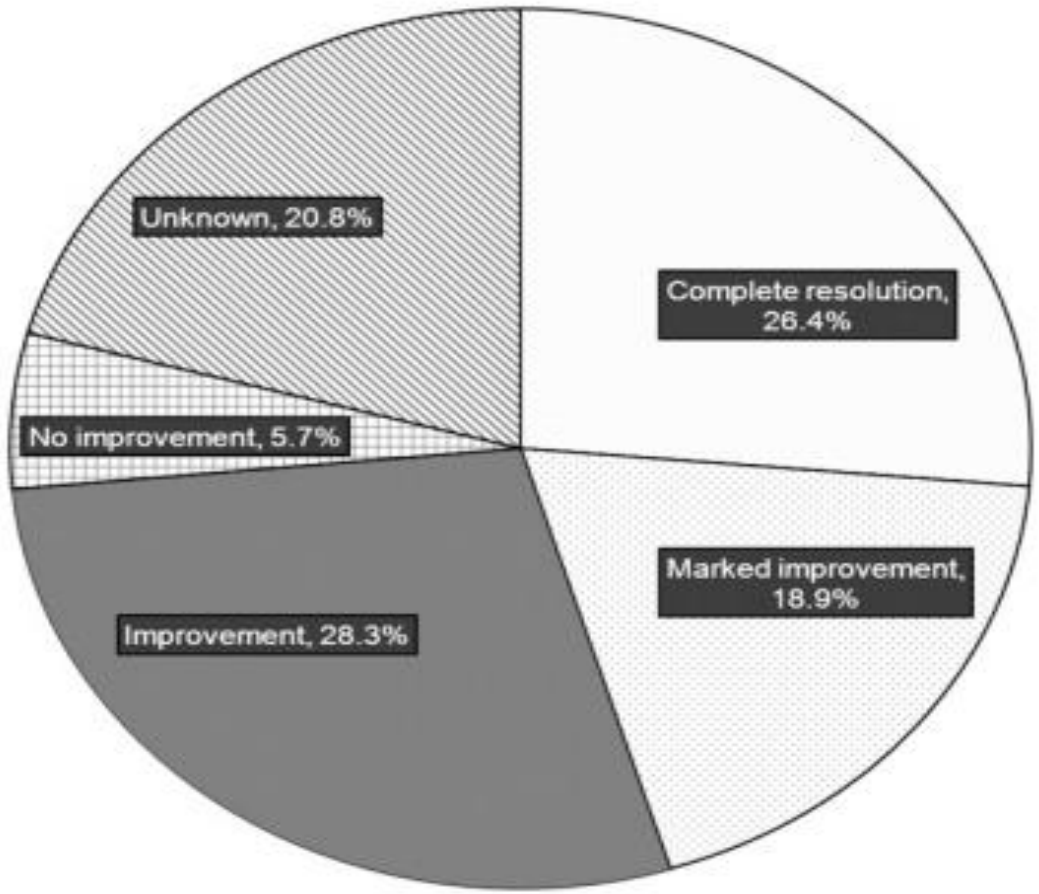
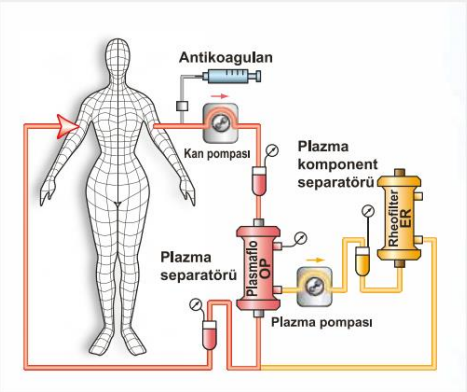


Figure 2. | Outcome of calcific uremic arteriolopathy in surveyed patients treated with sodium thiosulfate.

Results

- One-year mortality in patients treated with STS was 35%. Adverse events, laboratory abnormalities, and weight-related changes were mild.
- Significant reductions in serum phosphorous (P=0.02) and parathyroid hormone (P=0.01) were noted during STS treatment in patients who completed the therapy
- Although conclusive evidence regarding its efficacy is lacking, a majority of patients who received STS demonstrated clinical improvement in this study.



RHRHEOFILTER

RheofilRheofilter™ ER-4000/Asahi Plasma Component Separator

Plasma component separator specifically designed for rheopheresis to treat *microcirculatory disorders*

Rheopheresis

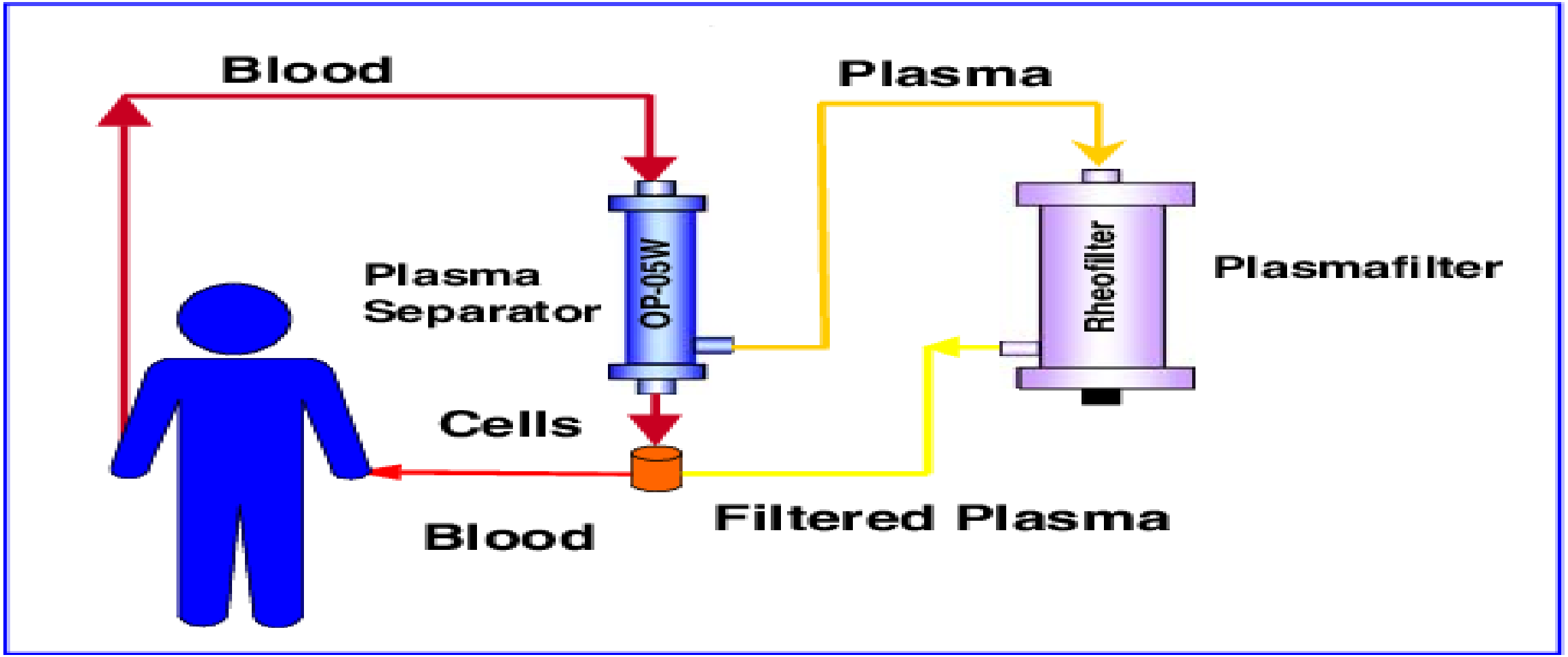
Rheopheresis

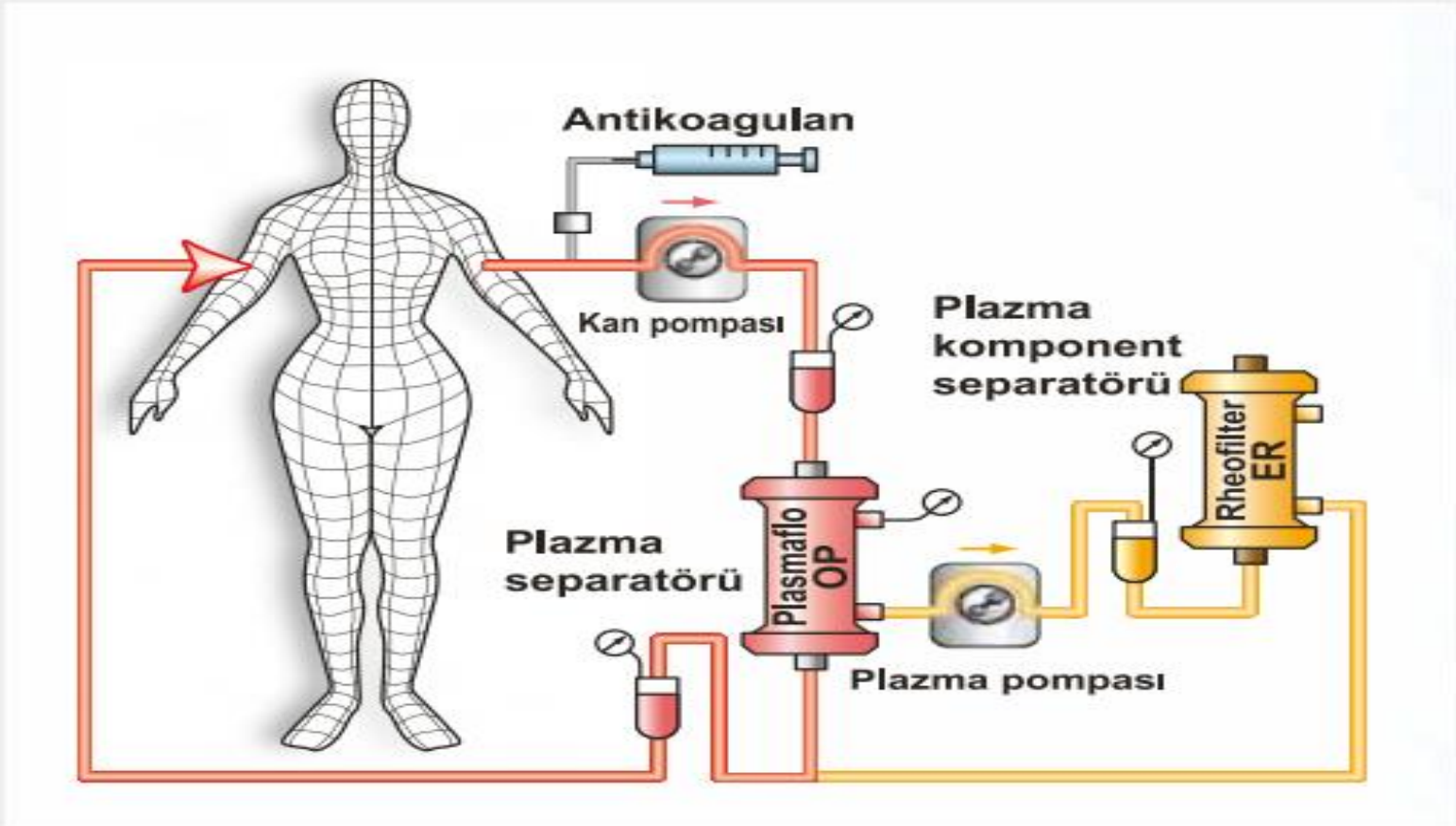
- Rheopheresis is an extracorporal selective double-filtration plasmapheresis**(DFPP)**
- In the first part of the treatment the blood is passes through the plasma filter, which separates blood cells from the plasma.
- Then the plasma flow to a second filter called MONET (Membranefiltration Optimised Novel Extracorporal Treatment).
- The MONET filter retains high molecular weight proteins such LDL, Lp(a), fibrinogen, α2 macroglobulin, vWF and IgM.
- Hereby the whole blood and plasma viscosity decrease, improves microcirculation, and has a positive effect on lipid profile as well.
- Accorging to ASFA recommendation rheopheresis is a first line treatment in age-related dry macular degeneration and in sudden sensorineural hearing loss.

Rheopheresis

- This Hypothesis is that the treatment of microcirculation by rheopheresis would improve wound healing of the ischemic lesion and/or reduce major amputation and thus the prognosis of the affected limb of the patient on hemodialysis.

- This objective is to demonstrate the efficacy of rheopheresis, (twelve sessions), to avoid major amputation and reaches complete wound healing of ischemic lesion in the dialysis patient population


Blood
Plasma
Plasma
Separator
OP-05W
Rheofilter
Plasmafilter
Cells
Blood
Filtered Plasma


Antikoagulan
Kan pompası
Plazma
komponent
separatörü
Rheofilter
ER
Plazma
separatörü
Plasmaflo
OP
Plazma pompası

RHEOFILTER

Rheofilter™ ER-4000/Asahi Plasma Component Separator

Plasma component separator specifically designed for rheopheresis to treat *microcirculatory disorders*

Rheopheresis

Plasma Volume to Process

•In general it's as estimated plasma volume (EPV) of the patient. EPV is calculated with below formula.
•EPV=BV x 1/13x (1-Hc/100)
•BW: body weight (kg)
•Hct: Hematocrit (%)
•Example: patient body weight = 65 kg, Hc: %40 EPV = 3 L

Rheopheresis

- Anticoagulant

Usually heparin or citrate (sodium citrate or ACD-A) is used as anticoagulant.

- Replacement Liquid

Replacement liquid is chosen depending on the patient's situation, cost, appropriateness and required volume for the removed plasma replacement during exchange therapy. Usually albümin and fresh frozen plasma (FFP) are used.

NEPHROLOGY

APSN

Original Article

Rheopheresis: A new therapeutic approach in severe calciphylaxis

Thomas Robert, Arnaud Lionet, Stanislas Bataille, Guillaume Seret

First published: 01 October 2019 | https://doi.org/10.1111/nep.13666 | Citations: 4

Volume 25, Issue 4
April 2020
Pages 298-304

- We report the use of rheopheresis, a double filtration apheresis technique, specifically designed to improve blood rheology and tissue perfusion, as adjunctive therapy in eight patients with severe CUA

Methods

- We retrospectively analysed eight cases of severe CUA treated by rheopheresis after failure of conventional measures, including administration of sodium thiosulfate and discontinuation of vitamin K antagonists.

Results

- Of the patients, there were 5 (63%) women, the median age was 69 (63.9-73) years. Four (50%) patients had biopsy-proven CUA. At diagnosis, the median dialysis vintage was 35 (3.9-42) months; five (63%) patients were anuric. Weekly median dialysis duration and dose were 12 (12-12.75) hours and 1.19 (1.13-1.48) Kt/V per dialysis session, respectively. Median time from CUA onset to first rheopheresis therapy was 26 (3.2-68) days. Patients started with 2-3 weekly sessions, coupled with haemodialysis. Complete remission was obtained in five patients (66%) after 25 (19-39) sessions over a duration of 119 (114-196) days. Three patients died, two of which resulted from an infectious complication related to CUA.
- **Conclusion**
- Rheopheresis is a promising approach, with a good safety profile, for the treatment of CUA. A prospective study with a larger population, would clarify its place in the therapeutic armamentarium


Nephrology, Dialysis and Renal Transplantation Department at
The Centre Hospitalier de Grenoble
Grenoble University Hospital Centre
Novartis
& The Jordanian Society of Nephrology & Renal Transplantation
invite you to attend the virtual meeting
Levant Kidney Transplant Upstart Classes
SESSION 3
Professor Lionel Rostaing
Dr. Paolo Malvezzi
October 22, 2020
7:00 pm (GMT +3)
"Apheresis and kidney transplantation."
Dr. Paolo Malvezzi
"Rheopheresis: Grenoble Faculty experience."
Prof. Lionel Rostaing

DFPP(*Double filtration plasmapheresis*) session Schedule

- 1st week: 2sessions = 2
- 2nd and 3rd weeks: 3 sessions = 6
- 4th and 5th weeks: 2 session = 4
- 6th to 23rd week: 1 session/week = 18
  - Total : 30 sessions over 6-month period

Pain and general status

- Huge decrease in major painkillers:
  - First 2 weeks: IV Paracetamol + IV Nefopam + Oxycodone
  - 3rd week: Nefopam + Oxycodone
  - 4th and 5th weeks: Nefopam +/- Oxycodone
  - 6th week onward: no more painkillers
  - Progressive increase in dry weight and improvement in well-being

Transcutaneous Oxygen Pressure (TcPO2) outcome

	Baseline	baseline	After 9 DEPP sessions	After 9 DEPP sessions
	Right	left	Right	Left
Forefoot	5	53	71	Amputated
Lower 1/3 calf	41	26	45	Amputated
Upper 1/3 calf	43	45	57	ND
thigh	44	82	ND	ND

Conclusion

- Rheopheresis is well tolerated
- Vascular access: easy for dialysis patients: more complicated in the case of non-ESRD patients
- Pheopheresis results in fast and huge improvement in pain
- Multidisciplinary coordination ++
- Pheopheresis may help postpone amputation
- TcPO2 monitoring
- Pheopheresis has to be implemented as early as possible in order to limit the size/level of amputation

summary

- Calcific uremic arteriolopathy (CUA) is an often fatal condition with no effective treatment
- diabetes mellitus; higher body mass index; higher levels of serum calcium, phosphorous, and parathyroid hormone; and nutritional vitamin D, cinacalcet, and warfarin treatments were associated with increased odds of subsequent CUA development.
- Once the diagnosis is made, calcium-containing supplements and vitamin D analogs should be discontinued, and non–calcium-based phosphorus-binders should be titrated for aggressive phosphorus control.
- Sodium thiosulfate, at a dose of 25 g IV three times per week, has been reported to completely resolve the lesions
- The treatment of microcirculation by rheopheresis would improve wound healing of the ischemic lesion and/or reduce major amputation of the affected limb of the patient on hemodialysis.


Thanks for
attention