Chandra et al., J Nephrol Therapeutic 2012, 2:1
DOI: 10.4172/2161-0959.1000114

Journal of Nephrology & Therapeutics

Review Article Open Access

Calciphylaxis – A Rare Devastating Condition Associated with Chronic Kidney Disease

Mathur Mahesh Chandra[1]*, Das G.C[2], Das gayatri[2] and Mathur Manik[3]

[1]Department of Dermatology, College of Medical Sciences & teaching Hospital,Bharat Pur, Chitwan, Nepal
[2]Department of Nephrology, College of Medical Sciences & teaching Hospital,Bharat Pur, Chitwan, Nepal
[3]City hospital (NHS), Nottingham, NG5 1PB, UK

Abstract

Calciphylaxis, a rare, life threatening disease, usually observed in patients with chronic kidney disease and characterised by typical skin lesions - violaceous, reticulate areas of cutaneous necrosis particularly in the extremities, raised calcium phosphorous product, elevated parathyroid hormone level, histopathologically skin biopsies shows mural calcification affecting small arterioles and radiographic evidence of blood vessel and soft-tissue calcification.

Calciphylaxis is a small-vessel vasculopathy, reported to occur in about 1-4% of haemodialysis patients. Disease is associated with a high mortality which ranges from 60–80% and relates to wound infection, sepsis and organ failure. Prolonged hyperphosphatemia and/or elevated calcium phosphorus products, Protein malnutrition, warfarin use and hypercoagulable states, such as protein C and/or protein S deficiency are associated with increased risk of the disease.

Clinically, many dermatologic conditions resemble the skin lesions of Calciphylaxis but can be discern by careful clinical evaluation of patient and histopathological examination of skin biopsy. Different therapeutic agents have been reported for the treatment of this condition with variable results. Therapeutic goals are guided by controlling levels of parathyroid hormone, calcium, phosphate, and the calcium-phosphate product within the normal range. A high index of suspicion and an active multidisciplinary management approach, with rigorous attention to wound care and prevention of sepsis, are vital steps in the management of these patients.

In this overview, we discuss the pathophysiology, clinical features, risk factors, and diagnosis and management issues relating to Calciphylaxis. This review is of interest to Medical specialist- specially to Dermatologist and Nephrologists for early identification of disease and therapeutic intervention.

Keywords: Calciphylaxis; Antiphospholipid syndrome; End stage renal disease

Introduction

Calciphylaxis is a rare but devastating condition characterised by metastatic calcification affecting small- and medium-sized vessels resulting in significant Cutaneous as well as systemic manifestations. It may cause ischemic necrosis of the dermis, subcutaneous tissue, muscle, fascia (Calciphylaxis cutis), and internal organs (visceral Calciphylaxis). Skin lesions typically occur over areas of high fat content, progressing to black leathery eschars and increased risk of infection, often leading to sepsis [1].

The current prevalence of the syndrome varies from 1% to as high as 4% of the dialysis population and these patients may develop some form of Calciphylaxis [2]. Calciphylaxis is associated with a high mortality rate, ranging from 46 to 80% and the most common complication and cause of death is local infection e.g., cellulitis, panniculitis, ischemic myopathy leading to sepsis and visceral involvement [3,4]

Classically, Calciphylaxis is commonly found in patients with end-stage renal disease on chronic maintenance dialysis or following renal transplantation [5]. In addition, numerous nonuremic conditions associated with Calciphylaxis, primary hyperparathyroidism. malignancies, including malignant melanoma [6], metastatic breast cancer [7], multiple myeloma [8] and leukemias [9]. Alcoholic liver disease and cirrhosis [10], autoimmune diseases, including systemic lupus erythematosus [11], rheumatoid arthritis [12], and Crohn's disease [13], Hypercoagulable states resulting from protein C and S deficiency [14], antiphospholipid syndrome [15], or obesity [16]. Various pharmacologic agents have also been implicated in causing Calciphylaxis, the most well-known being glucocorticoids[17], high-dose vitamin D and its analogues (e.g., calcitriol) [1], and warfare [18].

In patients with end-stage renal disease (ESRD), calcium-based phosphate binders, calcium absorption from dialysate, the widespread use of oral phosphate binders to combat uremic osteodystrophy has been implicated as a causative factor in accelerating uremic vasculopathy in the dialysis population [5]. Attention to mineral metabolism is vital in the management of patients with renal disease. High index of suspicion, early recognition and timely appropriate intervention as well as an active multidisciplinary approach are mandatory for management of Calciphylaxis. In presence of typical skin lesion or absence of cutaneous lesions in a high-risk patient, Calciphylaxis should be suspected and the Clinician should be vigilant of the possibility of visceral involvement. Screen for systemic symptom is warranted

History

Bryant and white in 1898, first described association between Cutaneous gangrene and vascular calcification [19]. The term Calciphylaxis, was coined by Selye and colleagues in 1962 as a condition of systemic hypersensitivity induced by sensitizing agents that resulted

***Corresponding author:** Mathur Mahesh chandra, Department of Dermatology, College of Medical Sciences & teaching Hospital, Bharat Pur, Chitwan, Nepal, E-mail: maheshmathur2@hotmail.com

Received November 03, 2011; **Accepted** January 04, 2012; **Published** January 06, 2012

Citation: Chandra MM, Das GC, gayatri D, Manik M (2012) Calciphylaxis – A Rare Devastating Condition Associated with Chronic Kidney Disease. J Nephrol Therapeutic 2:114. doi:10.4172/2161-0959.1000114

in metastatic calcification in various organs upon rechallenging, which was analogues to the anaphylaxis. Pioneer experimental work showed cutaneous calcification and necrosis upon rechallenging with egg white, metallic salts and local trauma [20]. Few years later, Coates et al. [21] proposed the term calcific uremic arteriolopathy (CUA) because experimental calcinosis is known to produce extra vascular rather than arteriolar/arterial calcification and not as that of Calciphylaxis [21].

Calciphylaxis as a syndrome was proposed by Gipstein et al. in 1976 and Winklemann and Keating described vascular calcification and cutaneous necrosis, developing on a background of hyperparathyroidism resulting from adenoma/carcinoma [22,23].

Pathophysiology

Pathophysiology of Calciphylaxis is poorly understood. Disease predominantly affects small- and medium-sized blood vessels and manifest as ischaemic necrosis. Association with increase calcium phosphorus product has been reported and may play crucial role in the pathogenesis of disease. The association between cutaneous gangrene and vascular calcification has been described since 1898 and calcification of cutaneous vasculature is known to be associated with chronic renal disease as well as multiple non uremic conditions with increase calcium phosphorus product [24], however, no significant difference was reported from control patient [25]. In patients with end-stage renal disease (ESRD), increased dietary calcium, calcium-based phosphate binders, calcium absorption from dialysate, abnormalities of bone buffering and turnover contribute to positive calcium balance. The widespread use of oral phosphate binders to combat uremic osteodystrophy has been implicated as a causative factor in accelerating uremic vasculopathy in the dialysis population [26].

The 'induced hypersensitivity' in Calciphylaxis resulting in local calcification following the two-step process of sensitizing and challenging is analogous to anaphylaxis, and has been propose as pathomechanism of the disease [20]. However, clinical appearance and the histopathogical findings of Calciphylaxis, differ in animal models. Moreover, experimental calcinosis is known to produce extra vascular rather than arteriolar/arterial calcification, hence the term calcific uremic arteriolopathy (CUA) was proposed [21]. Vascular calcification and cutaneous necrosis, developing in patient with hyperparathyroidism resulting from adenoma/carcinoma has been reported in literature [23], suggesting its role in pathogenesis of the disease.

Reported mineral abnormalities do not explain the process of thrombosis leading to ischemia and significantly low functional levels of protein C has been reported in patients with Calciphylaxis [14,27]. This suggest role played by Protein C and S in the pathogenesis of the disease. However, there is no total agreement on this issue as low levels persisted even when lesions were healing [28].

Several non-collagenous proteins are reported to play key roles in the pathogenesis of calcification apart from mineral disbalance. Studies have revealed glycoproteins such as matrix Gla protein (MGP) and osteopontin (OPN), in pathological arteries and support the role of these proteins in the development of vascular fibrosis and calcification [29,30]. Staining for OPN demonstrated positivity within calcific foci in arteries, arterioles, and capillaries and not detected in the absence of calcification. Similarly, MGP was localized to calcific foci and was not detected in non-calcified vessels. OPN and MGP are also up-regulated in the microvasculature in Calciphylaxis. MGP contains five c-carboxylated glutamic acid residues, which has a high affinity for calcium, phosphate, and hydroxyapatite and studies have shown that MGP regulates both vascular cell differentiation and vascular calcification [29] MGP is up-regulated at sites of calcification and may be an attempt to 'clear' calcium from the vessel wall. Alternatively, MGP present in these vessels may be non-functional due to deficiencies in either c-carboxylase and/or vitamin K. this support the view that warfarin therapy may be a risk factor for the development of ischaemic tissue necrosis in Calciphylaxis, as this drug results in the production of non-functional MGP.

Alpha 2-Heremans-Schmid glycoprotein/fetuin A (ahsg/fetuin) [31] (a serum protein, produced by the liver in adults) has been shown to play a preventive role in the pathogenesis of calcification and this protein is known to act systemically to inhibit ectopic calcification. Furthermore, fetuin-A knock-out mice are known to develop extra-skeletal calcification in the presence of hypercalcaemia, demonstrating that this protein plays a key role in the inhibition of calcification. Normalization of impaired inhibition of hydroxyapatite precipitation following addition of fetuin-A to the serum of dialysis patients having Calciphylaxis has been demonstrated [31].

Recently, Bone proteins are incriminated to involve in the pathogenesis and are reported to express in calcified arteries in patients with calciphylaxis [32] Bone morphogenic protein-4 (BMP-4), which is physiologically involved in bone metabolism, is considered to play a role as a promoter of vascular medial calcification [33]. Further studies at sub cellular level may unearth the basic pathophysiology of Calciphylaxis.

Clinical Manifestations

It has been estimated that the incidence of new cases of Calciphylaxis is 1 case per 100 haemodialysis patients per year [2].

Risk/trigger factors for Calciphylaxis include renal impairment, female, Caucasian race, obesity, warfarin use, hypercoaguable states, diabetes mellitus, dialysis dependency, protein malnutrition and those receiving calcium salts and vitamin D therapy, Albumin infusions as well as subcutaneous insulin injections have been reported to precipitate calciphylaxis [5,34].

The cutaneous lesions of Calciphylaxis have a characteristic clinical appearance and Skin lesions typically occur over areas with high adipose tissue content that includes abdomen, thighs, lateral and posterior calves, and buttocks.

Initial skin lesions appear as red subcutaneous nodules or violaceous plaques, often in a livedo reticular pattern that progress to areas of central ischemic necrosis. Bullae may be present over the lesions and is a predictor of impending necrosis. As lesions increase in size over weeks or months, ecchymoses and indurated subcutaneous nodules extend beyond the area covered by the superficial lesions. Late-stage lesions appear as black, deeply ulcerated, leathery eschars (Figure 1) that extend down to the fascia and are very vulnerable to secondary infection. Gangrenous change may be observed in distal appendages such as the fingers, toes, and penis. Patients may present with indurated plaques without ulceration [35] at each stage of progression, the lesions are extremely painful. Violaceous, mottled, painful cutaneous lesions should alert clinicians to the possibility of Calciphylaxis. Vasculitic syndromes, cholesterol embolization syndrome, cryoglobulinaemia,

cryofibrinogenaemia, warfarin-induced skin necrosis and disseminated intravascular coagulation (DIC) may present with cutaneous features similar to that of Calciphylaxis and should be consider in differential diagnosis.

Extra-cutaneous Calciphylaxis has been described. Ischemic necrosis occurring at the fingers and toes[36], adjacent muscles [37], breasts [38], tongue [39], and penis [40] have been reported. Acute calcification of major organs such as the heart and lungs have been reported, the latter being a cause of acute respiratory failure in these patients. Intractable cardiac failure may follow renal transplantation as a result of cardiac calciphylaxis [41,42] calcific cerebral embolism is a recognized cause of neurological symptoms in patients with chronic renal disease [43].

Diagnosis

Clinically, Calciphylaxis mimic many dermatologic disorders that warrant skin biopsy to differentiate. However, there is a risk of inoculating or spreading infection and poor wound healing of wound. Overall assessment of health status of the patient is mandatory before proceeding for biopsy. A 4–6 mm punch biopsy with ample subcutaneous tissue from the centre of the black eschar usually reveals the disease; however, a deep incisional biopsy may be necessary.

Skin biopsy revel extensive calcification of the tunica media of small- and medium-sized dermal and subcutaneous arterioles (Figure 2). Intraluminal fibrin thrombi, subintimal fibrosis, and endothelial cell injury in the absence of vasculitic changes and a prominent inflammatory infiltrate, although nonspecific, may also indicate Calciphylaxis. These histological findings should be differentiated from those of Mönckeberg medial calcific sclerosis, which mainly occur in the tunica media of medium-sized muscular arteries, are not accompanied by changes in the surrounding subcutaneous tissue. Where facilities available,Electron microscopic studies may be helpful in distinguishing calcium and phosphorous deposits from other trace metals (e.g., aluminium, iron, magnesium), capable of precipitating in the tunica media [34].

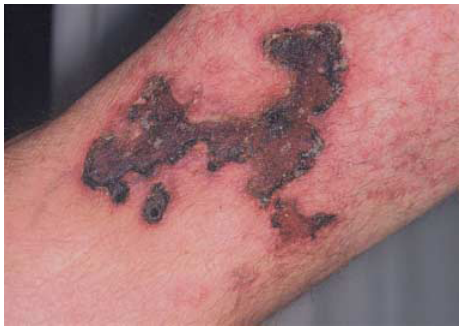

Figure 1: Showing skin lesion of Calciphylaxis-escher formationz.

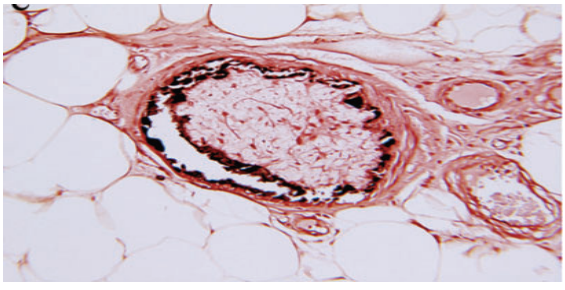

Figure 2: Showing Intemal Calcification of subcutaneous blood vessel (Von Kossa staining X100)

Imaging study also plays a role in the diagnosis of Calciphylaxis; however, Radiographic imaging is generally nonspecific and demonstrates vascular calcification in late-stage of the disease. Non-invasive and less painful alternative for identifying deeper lesions in sonography, which shows diffuse parenchymal edema, skin thickening, and numerous echogenic foci with posterior acoustic shadow are suggestive of calcification [44].

Recently, nuclear bone scans have been reported as promising diagnostic tool for calciphylaxis [45]. Specifically for detecting subcutaneous calcium deposits and successfully utilized to reveal the extent of systemic involvement as well as for the follow up of the case. Several laboratory tests have been shown to be correlated with diagnosis of Calciphylaxis and are essential in its management. Serum calcium, phosphate, elevated blood urea nitrogen and creatinine and parathyroid hormone levels may provide insight in the etiology of Calciphylaxis. If an open wound is present, cultures should be obtained to detect early infection. Other laboratory findings associated with Calciphylaxis include hyperphosphatemia, elevated erythrocyte sedimentation rate (ESR), hypoalbuminemia, and elevated alkaline phosphatase levels.

Management of the Patients

Management of Calciphylaxis involves a multidisciplinary approach consisting of primary prevention, wound care and infection prophylaxis, controlling disease progression, and treatment of the systemic disease. Although a standard protocol for the treatment of Calciphylaxis has not been developed, various treatment options reported in literature with variable outcome. It is important to emphasize disease prevention i.e., by early identifying and treating renal disease with specific attention to calcium-phosphate homeostasis. An in-depth assessment of co morbid conditions, risk factors and clinical evaluation of the sites at which the skin lesions tend to occur is often rewarding

Wound care, avoidance of trauma, and appropriate antibiotic usage together with nutritional support and adequate pain control are important aspects of general care of these patients. In the initial stages when skin is eroded, gentle handling is important and careful dressing of wounds with material such as petrolatum-impregnated gauze help to minimize tissue damage. Debridement and skin grafting may be warranted, however, the role of debridement is controversial and it has been suggested that debridement is contraindicated for wounds covered with dry, non-infected eschars [46]. Prevention of systemic infection is vital aspect of the management. Transcutaneous oxygen tension (TCPO2) measurement has been used as a rapid non-invasive screening for skin ischemia before the development of skin lesions [47].

Systemic Therapy for Calciphylaxis has generally been guided by controlling levels of parathyroid hormone, calcium, phosphate, and the calcium-phosphate product within the normal range and this is usually achieved by treating the underlying cause of hyperparathyroidism through medical therapy or partial or total parathyroidectomy.

The first-line treatment of Calciphylaxis without hyperparathyroidism is sodium thiosulphate. Sodium thiosulphate is a potent antioxidant protecting endothelial cell as well as a chelator of calcium. The therapeutic effect of sodium thiosulphate is as a result of its ability to dissolve calcium deposits in tissue into soluble calcium thiosulphate complexes. The common dose of sodium thiosulphate is 25 g administered intravenously three times per week following dialysis. Rapid pain relief and successful wound healing within weeks to months of initiating therapy has been reported. In some cases, complete resolution of lesions has been reported [48]

The medical therapies for Calciphylaxis secondary to hyperparathyroidism include cinacalcet and bisphosphonates. Cinacalcet, a calcimimetic agent, has the unique ability to lower parathyroid hormone, calcium, and phosphate levels, thus effectively regulates the calcium-phosphate product [49]. Bisphosphonates such as palmidronate have been shown to have direct inhibitory effect on arterial calcification as well as anti-inflammatory properties. Daily oral doses of cinacalcet 30 mg, with increases in dose as tolerated to a maximum of 60–120 mg, and daily oral doses of etidronate disodium 200 mg for 14 days or intravenous administration of pamidronate 30 mg every 2 weeks during dialysis have shown promising results in pain control and promoting wound healing [50]. However, bisphosphonates predominantly undergo renal excretion and must be used with caution in patients with Chronic Kidney disease. Systemic toxicities such as impaired bone metabolism (e.g., osteonecrosis of the jaw) may occur.

Surgical intervention such as parathryroidectomy, total or subtotal is reported to be curative intervention which enables tight control of calcium and phosphate metabolism and associated with resolution of pain, wound healing and a longer median survival in patients with Calciphylaxis [51]. Given the risks of surgery and the poor health condition of Calciphylaxis patients, parathyroidectomy is indicted in refractory cases to medical management. In select cases, when Calciphylaxis manifests as breast disease, partial or total mastectomy may be recommended to the patient for symptomatic treatment. Revascularization and amputation may have to be resorted in cases where all other supportive and conservative measures have failed.

Intravenous maxacalcitol, a vitamin D [3] formulation, used in conjunction with percutaneous ethanol injection therapy (PEIT) has been documented to reduce PTH secretion, regression of parathyroid hyperplasia and control of the calcium-phosphorous product in dialysis patients and this combination is also considered as preventative measure in vascular calcification in the dialysis population [52].

Calcium- and aluminium-free phosphate binders such as sevelamer hydrochloride (RenaGel) have been found to be useful in the management of the patient. Haemodialysis patients treated with sevelamer were found to be protected from calcification of the aorta and coronary arteries [53].

Certain modalities of treatments have been reported in selective Calciphylaxis patients. The most popular is hyperbaric oxygen therapy, which counteracts tissue hypoxia by supplying high concentrations of oxygen. Benefit has been shown in patients who underwent repeated treatment (range 20–108 sessions, generally 20 through 40) with 100% oxygen applied at 2.5 standard atmospheres for 90 minutes [54]. Visible ulcer healing was observed between 3 and 7 weeks after initiating therapy. In claustrophobic patients hyperbaric oxygen therapy may not be suitable as it is conducted in a confined chamber.

Use of 1 mg/kg enoxaparin (low molecular weight heparin) twice daily demonstrated efficacy in Calciphylaxis ulcer healing specially, in case of Calciphylaxis presenting with a clinically hypercoagulable state (history of multiple deep venous thromboses, low protein C, low antithrombin III). Benefit from intravenous administration of 10 mg tissue plasminogen activator (tPA) for 14 days have been reported [55].

The newest therapeutic modality for Calciphylaxis treatment is 'Combination therapy'. Combination therapy is naturally more effective than single-agent therapy alone if the agents act synergistically (e.g., preventing calcium deposition and preventing tissue hypoxia). At least one study has demonstrated the benefits of using sodium thiosulphate in combination with hyperbaric oxygen therapy, although it has not been compared with single-agent therapy [56]. The efficacy of other combination therapies such as sodium thiosulphate with cinacalcet and sodium thiosulphate with bisphosphonates are currently being investigated.

Prognosis

Prognosis of Calciphylaxis is frequently poor once disease is diagnosed. Uncontrolled sepsis being the lethal event in most cases [57]. The most common complication and cause of death is local infection (e.g., cellulitis, panniculitis, ischemic myopathy) leading to sepsis and organ failure. Gangrene is a common sequence and amputation often required. Prognosis is, however; generally better for patients with lesions on the extremities compared with those having lesions on the trunk, or visceral organ involvement. Factors associated with poor overall prognosis include late intervention, skin lesions involving the trunk, ulceration of skin lesions, female gender, increased weight, and the need for vascular surgical intervention and an extended period in hospitalization is normal with a high morbidity in those patients who survive.

Conclusion

Calciphylaxis is a potential lethal syndrome. A high index of suspicion, an early active multidisciplinary intervention medical and/or surgical are vital for the management. Multiple risk and triggering factors associated with the pathogenesis of this disease remains focus of future research. HBO, sodium thiosulphate, biphosphonates, and low dose tissue plasminogen activator therapy offer potential therapeutic options for patients with Calciphylaxis. Aggressive treatment of infection and stabilization of calcium phosphate product remains important components of management strategies.

The pathogenesis of Calciphylaxis will be better understood in future and targeted molecular therapies specially, two possible molecular targets - Fetuin-A and Matrix Gla - the vascular calcification inhibitors will be available for the treatment. However, further studies are necessary to determine the true value of these novel treatments [31,48].

Moreover, Calciphylaxis is largely unknown outside of Dermatology, Nephrology, Rheumatology, and Vascular surgery, Clinicians in these specialties should make an effort to educate the medical community regarding prevention, early detection, and treatment of this severe fatal condition

References

1. Arseculeratne G, Evans AT, Morley SM (2006) Calciphylaxis: a topical overview. J EurAcad dermatol Venereol 20: 493-502.

2. Angelis M, Wong LL, Myers SA, Wong LM (1997) Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery 122: 1083-1089.

3. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR (2007) Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 56: 569-579.

4. Adrogue HJ, Frazier MR, Zeluff B, Suki WN (1981) Systemic calciphylaxis revisited. Am J Nephrol 1: 177–183.

5. Mazhar A. Rauf, Johnson J R, Daniel Gillen, Stivelman J, Ryan M J, et al. (2001) Risk factors and mortality associated with calciphylaxis in end-stage renal disease, Kidney Int 60: 324-3322.

6. Kutlu NO, Aydin NE, Aslan M, Bulut T, Ozgen U, et al. (2003) Malignant melanoma of the soft parts showing calciphylaxis. Pediatr Hematol Oncol 20: 141-146.

7. Mastruserio DN, Nguyen EQ, Nielsen T, Hessel A, Pellegrini AE (1999) Calciphylaxis associated with metastatic breast carcinoma. J Am Acad Dermatol 41: 295-298.

8. Crippa C, Ferrari S, Drera M, Ferrari S, Drera M, et al. (2010) Pulmonary calciphylaxis and metastatic calcification with acute Respiratory Failure in Multiple Myeloma. J Clin Oncol 28: 133-135.

9. Goff HW, Grimwood RE (2005) A case of calciphylaxis and chronic myelomonocytic leukemia. Cutis 75: 325-328.

10. Ferreres JR, Marcoval J, Bordas X, Moreno A, Muniesa C, et al. (2006) Calciphylaxis associated with alcoholic cirrhosis. J Eur Acad Dermatol Venereol 20: 599-601.

11. Sakr SH, Russell EB, Jasin HE (2004) Systemic lupus erythematosus and calciphylaxis. J Rheumatol 31: 1851-1853.

12. Korkmaz C, Dundar E, Zubaroglu I (2002) Calciphylaxis in a patient with rheumatoid arthritis without renal failure and hyperparathyroidism: the possible role of long-term steroid use and protein S deficiency. Clin Rheumatol 21: 66-69.

13. Barri YM, Graves GS, Knochel JP (1997) Calciphylaxis in a patient with Crohn's disease in the absence of end-stage renal disease. Am J Kidney Dis 29: 773-776

14. Mehta RL, Scott G, Sloand JA, Francis CW (1990) Skin necrosis associated with acquired protein C deficiency in patients with renal failure and calciphylaxis. Am J Med 88: 252-257.

15. Wong JJ, Laumann A, Martinez M (2000) Calciphylaxis and antiphospholipid antibody syndrome. J Am Acad Dermatol 42: 849

16. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR (2007) Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 56: 569-579.

17. Ozbalkan Z, Calguneri M, Onat AM, Ozturk MA (2005) Development of calciphylaxis after long-term steroid and methotroxate use in a patient with rheumatoid arthritis. Intern Med 44: 1178-1181.

18. Asobie N, Wong E, Cook MG (2008) Calciphylaxis in a diabetic patient provoked by warfarin therapy. Clin Exp Dermatol: 33: 342-344.

19. Bryant JH, White WH (1899) A case of calcification of the arteries and obliterative endarteritis associated with hydronephrosis in a child aged six months. Guys Hosp Rep 55: 17-28.

20. Selye H (1962) Calciphylaxis. University of Chicago Press, Chicago.

21. Coates T, Kirkland GS, Dymock RB, Murphy BF, Brealey JK, et al. (1998) Cutaneous necrosis from calcific uremic arteriolopathy. Am J Kidney Dis 32: 384-391.

22. Gipstein RM, Coburn JW, Adams DA, Lee DB, Parsa KP et al. (1976) Calciphylaxis in man- A Syndrome of Tissue Necrosis and Vascular Calcification in 11 Patients With Chronic Renal Failure, Arch Intern Med 136: 1273-1280.

23. Winklemann RK, Keating FR (1970) Cutaneous vascular calcification, gangrene and hyperparathyroidism. Br J Dermatol 83: 263-268.

24. Kossard S, Winklemann RK (1979) Vascular calcification in dermatopathology. Am J Dermatopathol1: 27-34.

25. BleyyerAJ, ChoiM, IgwemezieB (1998) A case study of Proximal Calciphylaxis. Am J Kedney dis 32:376-383

26. Igaki N, Moriguchi R, Hirota Y, Sakai M, Akiyama H, et al. (2001) Calciphylaxis in a patient with end-stage renal disease secondary to systemic lupus erythematosus associated with acral gangrene and mesenteric ischemia. Intern Med 40: 1232-1237.

27. Goldsmith DJ (1977) Calciphylaxis, thrombotic diathesis and defect in coagulation regulation. Nephrol Dial.Transplant 12: 1082-1083.

28. Perez-mijares R, Gumain-zamudio J, Payan-Lopez J, Rodriguez-Fernandez A, Gomez-Fernandez P, et al. (1996) Calciphylaxis in Haemodialysis Patients, functional protein S deficiency ? Nephrol Dial Transplant 11: 1856-1859.

29. Canfield AE, Farrington C, Dziobon MD, Boot-Handford RP, Heagerty AM, et al. (2002) The involvement of matrix glycoproteins in vascular calcification and fibrosis: an immunohistochemical study. J Pathol 196: 228-234.

30. Wesson JA, Johnson RJ, Mazzali M, Beshensky AM, Stietz S, et al. (2003) Osteopontin Is a Critical Inhibitor of Calcium Oxalate Crystal Formation and Retention in Renal Tubules, Jam Soc Nephrol 14: 139-147.

31. Schafer Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, et al. (2003) The serum protein alpha 2-Heremans Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 112: 357-366.

32. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, et al. (2002) Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int 61: 638-647.

33. Griethe W, Schmitt R, Jurgensen JS, Bachmann S, Eckardt KU, et al.(2003) Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. J Nephrol 16: 728-732.

34. Wilmer WA, Magro CM (2002) Calciphylaxis; emerging concepts in prevention, diagnosis and treatment. Semin Dial 15: 172-186.

35. Scheinman PL, Helm KF, Fairley JA (1991) Acral necrosis in a patient with chronic renal failure, Calciphylaxis. Arch Dermatol 127: 248-249, 251-242.

36. Edelstein CL, Wickham MK, Kirby PA (1992) Systemic calciphylaxis presenting as a painful, proximal myopathy. Postgrad Med J 68: 209-211.

37. Loynes JT (1999) A rare cause of breast necrosis, Calciphylaxis. Postgrad Med 106: 161-162.

38. Bedoya RM, Gutierrez JL, Mayorga F (1997) Calciphylaxis causing localized tongue necrosis: a case report. J Oral Maxillofac Surg 55: 193-196.

39. Karpman E, Das S, Kurzrock EA (2003) Penile calciphylaxis: analysis of risk factors and mortality. J Urol 169: 2206-2209.

40. Nahm WK, Badiavas E, Touma DJ, Wilkel CS, Falanga V (2002) Calciphylaxis with peau d'orange induration and absence of classical features of purpura, livedo reticularis and ulcers. J Dermatol 29: 209-213.

41. Matsuo T, Tsukamoto Y, Tamura M (2001) Acute respiratory failure due to 'pulmonary calciphylaxis' in a maintenance haemodialysis patient. Nephron 87: 75-79.

42. Kloeppel R, Luebke P, Mittag M ,Harald A, Susann S, et al. (2001) Acute hypercalcaemia of the heart ('bony heart'). J Comput Assist Tomogr 25: 407-411.

43. Katsamakis G, Lukovits TG, Gorelick PB (1998) Calcific cerebral embolism in systemic calciphylaxis. Neurology 51: 295-297

44. Bukhman R, Scheri RP, Selim MA, Baker JA (2010) Sonography in the identification of calciphylaxis of the breast. J Ultrasound Med 29: 129-133.

45. Soni S, Leslie WD (2008) Bone scan findings in metastatic calcification from calciphylaxis. Clin Nucl Med 33: 502-504.

46. Martin R (2004) Mysterious calciphylaxis: wounds with eschar – to debride or not to debride. Ostomy Wound Manage 50: 64-66.

47. Wilmer WA, Voroshilova O, Singh I, Middendorf DF, Cosio FG (2001) Transcutaneous oxygen tension in patients with calciphylaxis. Am J Kidney Dis 37: 797-806.

48. Cicone JS, Petronis JB, Embert CD, Spector DA (2004) Successful treatment

of calciphylaxis with intravenous sodium thiosulphate. Am J Kidney Dis 43: 1104-1108.

49. Sharma A, Burkitt-Wright E, Rustom R (2006) Cinacalcet as an adjunct in the successful treatment of calciphylaxis. Br J Dermatol 155: 1295-1297.

50. Schliep S, Schuler G, Kiesewetter F (2008) Successful treatment of calciphylaxis with pamidronate. Eur J Dermatol 18: 554-556.

51. Girotto JA, Harmon JW, Ratner LE, Nicol TL, Wong L, et al

52. E ctopic calcification is a frequent complication of many degenerative diseases. Here we identify the serum protein α_2–Heremans-Schmid glycoprotein (Ahsg, also known as fetuin-A) as an important inhibitor of ectopic calcification acting on the systemic level. Ahsg-deficient mice are phenotypically normal, but develop severe calcification of various organs on a mineral and vitamin D–rich diet and on a normal diet when the deficiency is combined with a DBA/2 genetic background. This phenotype is not associated with apparent changes in calcium and phosphate homeostasis, but with a decreased inhibitory activity of the Ahsg-deficient extracellular fluid on mineral formation. The same underlying principle may contribute to many calcifying disorders including calciphylaxis, a syndrome of severe systemic calcification in patients with chronic renal failure. Taken together, our data demonstrate a critical role of Ahsg as an inhibitor of unwanted mineralization and provide a novel therapeutic concept to prevent ectopic calcification accompanying various diseases.

53. . (2001) Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. Surgery 130: 645-650.

54. Tanaka M, Itoh K, Matsushita K, Matsushita K, Fukagawa M (2005) Combination therapy of intravenous maxacalcitol and percutaneous ethanol injection therapy lowers serum parathyroid hormone level and calcium X phosphorous product in secondary hyperparathyroidism. Nephrol Clin Pract 102: 1-7.

55. Chertow GM, Burke SK, Raggi P (2002) Sevelamer attenuates the progression of coronary aortic calcification in hemodialysis patients. Kidney Int 62: 245-252.

56. Basile C, Montanaro A, Masi M, Pati G, De Maio P, et al. (2002) Hyperbaric oxygen therapy for calcific uremic arteriolopathy – a case series. J Nephrol 15: 676-680.

57. Sewell LD, Weenig RH, Davis MD, McEvoy MT, Pittelkow MR (2004) Low-dose tissue plasminogen activator for calciphylaxis. Arch Dermatol 140: 1045-1048.

58. Rogers NM, Coates PT (2010) Calcific uremic arteriolopathy- the argument for hyperbaric oxygen and sodium thiosulfate. Semin Dial 23: 38-42.

59. Adrogué HJ, Frazier MR, Zeluff B, Suki WN (1981) Systemic calciphylaxis revisited. Am J Nephrol 1: 177-83.

60. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, et al (1997) Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Natur 386: 78-81.