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Review

Calciphylaxis: Epidemiology, Pathophysiology and Therapeutic Options

Ketteler Markus and Biggar Patrick

Division of Nephrology, Klinikum Coburg, Coburg, Germany

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Introduction

Calciphylaxis is a rare, but potentially life-threatening syndrome characterized by progressive and painful skin ulcerations associated with media calcification of medium-size and small cutaneous arterial vessels. Calciphylaxis primarily affects patients on dialysis or after renal transplantation, however, exceptions have been reported in patients with normal renal function and in association with chronic-inflammatory disease, malignancy or primary hyperparathyroidism. Clinical manifestation of calciphylaxis is associated with high mortality of up to 80%, superinfection of necrotic skin lesions with subsequent sepsis significantly contributing to this dramatic outcome. However, many calciphylaxis patients also suffer from advanced cardiovascular disease characterized by severe calcifications of larger arterial vessels. There are currently no exact numbers on the incidence of calciphylaxis available. Based on small international surveys, incidence is estimated to be in the range of 1:1.000 to 1:1.500 cases in patients on chronic renal replacement therapy per year, but there is good reason to suspect underrecognition caused by mild cases or misdiagnosis in a relevant percentage of patients.

The clinical picture of calciphylaxis

The term calciphylaxis was coined in 1962 by Selye in analogy to the term "anaphylaxis": His group was able to reproducibly induce skin calcifications by combining local trauma with additional "challenges" (inductors such as parathyroid hormone (PTH), active vitamin D, hypercalcemia) [1]. Nowadays, calciphylaxis, or its synonym calcific uremic arteriopathy (CUA), describes a clinical entity starting with indurated and very painful cutaneous plaques, sometimes in the local setting of a livedo reticularis. The syndrome frequently develops in the lower extremities (figure 1), but may also manifest around the abdomen and hips and may affect peripheral sites (e.g., finger tips) or even skeletal muscle [2-5]. In case reports, lesions on the penis, breasts and in visceral organs were also documented. Especially those lesions located at the distal extremities often raise suspicion of differential diagnoses of vasculitis, diabetic ulcerations or cholesterol emboli. Exulceration can occur very rapidly and progressively cover large skin regions, with significantly impaired wound healing capacity. The key complication is superinfection of such necrotizing areas. The histopathological hallmark of calciphylaxis is media calcification of cutaneous arterioles, but also of neural sheats and adipose tissues [6]. If treatment is not initiated early or remains unresponsive, these ulcerations worsen progressively and superinfections cause deleterious septic disease courses.

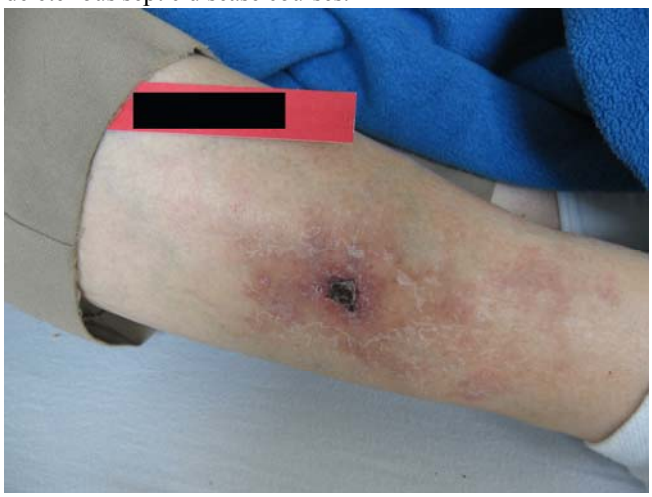

Fig. 1. Typical calciphylaxis lesion showing a painful, indurated, necrotic ulcer on the right leg of a 69-year-old female diabetic hemodialysis patient, surrounded by livedo reticularis. The patient had been hyperphosphatemic (P 2.21 mmol/L) and on warfarin treatment when the lesion occurred (photograph kindly provided by Dr. Christian Wulff, Erlangen, Germany).

Due to the relative rarity of calciphylaxis, there are no systematic analyses of standardized clinical diagnostic tests. The painful character of the lesions and the association with advanced renal disease can, however, be regarded as very characteristic features. Under debate is the role of skin biopsy to confirm the diagnosis of calciphylaxis. On the one hand, there are concerns that additional microtraumatization caused by biopsy may by itself induce a new focus of ulceration and worsen the disease course. On the other hand, biopsy is the only way to ascertain the diagnosis of calciphylaxis and to exclude other entities such as vasculitis. However, it is imperative to actively look for the pathognomic arteriolar calcifications by staining based on silver nitrate („von Kossa" staining) or alizarin red, because standard staining may not demonstrate media calcification of small arteries. Vice versa, skin biopsy obtained from patients with suspected vasculitis should probably also be actively evaluated to exclude calciphylaxis. Biopsy sites should preferably be at the margins of ulcers. If large areas are present,

Correspodence to: Markus Ketteler, Medizinische Klinik III, Klinikum Coburg, Ketschendorfer Str. 33, 96450 Coburg, Germany; Tel.: +49-(0)9561-249611; Fax.: +49-(0)9561-249612; E-mail: markus.ketteler@klinikum-coburg.de

bone scintigraphy may be an effective non-invasive diagnostic tool showing tracer deposition in calcified subcutaneous areas.

Risk factors

Data concerning the epidemiology of calciphylaxis is limited. The two most comprehensive publications are case-control studies comprising 19 and 36 patients [3,7]. Summarizing the results, female gender, diabetes mellitus, peritoneal dialysis, obesity, hypalbuminemia in the context of malnutrition and chronic inflammation, hyperphosphatemia, elevated calcium x phosphorous product and combined use of active vitamin D analogues with high doses of calcium-containing phosphate binders appear to be risk factors associated with calciphylaxis manifestation (Table 1). In case reports, calciphylaxis episodes were repeatedly reported in association with derangements of the calcium x phosphorous product in the context of severe secondary or tertiary hyperparathyroidism [4]. Along this line, some case reports and a recently published case series from the University of Wisconsin have demonstrated dramatic improvements of calciphylaxis following "emergency" parathyroidectomy; however, some reports have described *de novo* calciphylaxis with severe disease courses in patients who were previously parathyroidectomized [2,4,8]. Both disorders, severe (tertiary) hyperparathyroidism (HPT) and adynamic bone disease (ABD) in patients with relative or absolute hypoparathyroidism, may cause elemental derangements in mineral metabolism predisposing for calciphylaxis: In both situations, calcium x phosphorous homeostasis is massively deranged, either due to increased bone turnover (as in HPT) or due to bone "paralysis" (as in ABD). It is thought that the inability of the bone to serve as a „calcium buffer" may create an environment favouring extraosseous soft-tissue calcifications. Finally, in a number of case reports, a connection between the use of vitamin K antagonists (warfarin etc.) and the development of calciphylaxis has been reported. The potential pathophysiological relevance of this observation will be discussed below [5,6]

Table 1. Confirmed and suspected risk factors for calciphylaxis

Confirmed risk factors[1]	Suspected risk factors
Chronic kidney disease (especially CKD 5D and patients after renal transplantation)	Vitamin K deficiency therapy with Vitamin K antagonists (phenprocoumon, warfarin)
Secondary / tertiary hyperparathyroidism	Fetuin-A deficiency
Hyperphosphatemia	Inflammation
Elevated calcium x phosphate product (e.g., combination of high-dose active vitamin D and Ca-containing phosphate binders)	Adynamic bone disease
Female gender	Deficiency of other calcification inhibitory systems (e.g., pyrophosphates)
Diabetes mellitus	Genetic factors?
Obesity	
	Hypalbuminemia

[1]Based on case-control studies and case reports.

Calciphylaxis and calcification inhibitors

In recent years, numerous observations support the assumption that dysregulation in the balance of local or systemic calcium-regulatory factors may be involved in the development of unwanted calcification processes in the body [9]. Current data focus on the importance of matrix Gla protein (MGP) and fetuin-A (α2-Heremans Schmid Glykoprotein, AHSG) as prototypic calcification inhibitors.

MGP is a 10 kD protein exclusively expressed in vascular smooth muscle cells (VSMC) and chondrocytes. This protein requires post-translational vitamin K-dependent γ-carboxylation for activation. Accordingly, warfarin treatment suppresses MGP activation. Knockout of the MGP gene in mice ($MGP^{-/-}$) causes severe media calcification of large arteries with subsequent rupture of the ossified aorta; $MGP^{-/-}$ mice actually die of internal arterial hemorrhage at the age of 6 – 8 weeks [10,11]. MGP acts purely as local inhibitor, systemic overexpression is not capable of counteracting arterial calcification induced by $MGP^{-/-}$ [10]. Analogously, media calcification can also be induced by treatment with vitamin K antagonists [12,13]. In rats, warfarin-induced vascular calcification can be partially reversed by feeding supraphysiological doses of vitamin K1 or K2 following withdrawal of warfarin, whereas calcification progresses when only low doses of vitamin K are fed [13].

The second potentially important calcification inhibitor with regard to the pathophysiology of calciphylaxis is fetuin-A. Fetuin-A is a 60-kD glycoprotein produced in the liver and probably the most potent circulating calcification inhibitor. Extracellular concentrations are as high as 0.5 – 1.0 g/l under normal conditions, fetuin-A represents a major proportion of the alpha2-band of serum electrophoresis [9,14]. Importantly, this glycoprotein is regulated as a negative phase protein, thus, in situations of acute or chronic inflammation, blood and tissue levels of this calcification inhibitor may drop significantly and deficiency may occur (15). Of note, most of the very rare cases of calciphylaxis in patients with normal renal function were reported in active chronic inflammatory diseases [16,17].

Fetuin-A knockout ($fetuin\text{-}A^{-/-}$) mice spontaneously develop massive organ and soft-tissue calcification [18]. A large proportion of patients on dialysis show fetuin-A serum levels below the normal range, and fetuin-A deficiency is related to increased all-cause and cardiovascular mortality in

this patient group [19,20]. In eight well-characterized calciphylaxis patients, we were able to detect very low fetuin-A serum levels (range: 0.09 – 0.25 g/l) in the context of highly elevated CRP levels [18].

Therapeutic options

Therapeutic approaches are limited in calciphylaxis. As pointed out above, the available data is restricted to case reports and small case-control studies, while prospective studies are not available. Once calciphylaxis is suspected or diagnosed in a uremic patient, the first therapeutic aim must be normalization of the calcium x phosphate product, i.e. by intensifying dialysis treatment, by using low dialysate calcium and by high-dose treatment with (preferably calcium-free) phosphate binders. Reduction or withdrawal of active vitamin D treatment must be considered depending on the corresponding levels of PTH and calcium x phosphorous product. In calciphylaxis patients with hyperparathyroidism and signs of high bone turnover, „emergency" parathyroidectomy must be considered immediately. However, in such patients administration of calcimimetics may represent an effective therapeutic alternative – promising case reports on this conservative intervention have been published recently [21]. Once progressive ulcerations and necrosis are observed, early broad-spectrum antibiotics should probably be initiated.

Some data are available concerning the use of sodium thiosulfate and of bisphosphonates in the treatment of calciphylaxis [22, 23]. Thiosulfate is available as a chelating agent indicated for the treatment of cyanide intoxication. On the one hand, it possesses a high affinity to calcium ions, which may interfere with calcium and phosphate precipitation producing soluble calcium thiosulfate which can potentially be removed by dialysis. On the other hand, thiosulfate may also interfere with the local inflammation process by antioxidant properties. Both concepts currently lack proof.

It is currently unclear, whether bisphosphonates interact with extraosseous calcification processes via their antiresorptive bone effects or via direct peripheral pyrophosphate-like effects at the tissue sites. Although case reports on beneficial effects of pamidronate in calciphylaxis patients have recently been published, caution is advised concerning uncritical use of bisphosphonates in this patient group unless ABD is excluded or highly unlikely, since ABD will be aggravated by these compounds, especially in renal failure patients.

In calciphylaxis patients on warfarin treatment, warfarin withdrawal and switch to heparin use is urgently recommended, despite a lack of clear-cut prospective clinical evidence. However, the biological plausibility that vitamin K antagonism favors vascular calcification is regarded as extremely relevant and subsequent vitamin K supplementation may have to be addressed by future studies in this patient group. Basile *et al*. reported on succesful hyperbaric oxygen therapy in a small number of calciphylaxis patients [24]. This approach is based on the attempt to improve wound healing in ischemic tissues. In this study, affected areas were exposed 100% oxygen under 2.5-fold elevated atmospheric pressure in a closed chamber for 90 minutes per session in order to significantly increase local oxygen pressure in the ulcerated and necrotic areas (number of session per patient ranged between 20 and 108). 8 out of 11 patients showed effective healing of calciphylactic ulcerations. Finally, Fine and Zacharias reported on 36 calciphylaxis patients in different stages of the disease and on successful glucocorticoid treatment in early, non-ulcerated stages [3]. However, with regard to the threat of superinfection, glucocorticoids should certainly be avoided in patients with advanced lesions because of their immunosuppressive properties. Table 2 summarizes the published therapeutic approaches.

Table 2. Therapeutic strategies in calciphylaxis patients

General approaches:
Lowering of calcium x phosphate product (by phosphate binders, increasing dialysis dose, reduction of calcium exposure, reduction or withdrawal of vitamin D therapy)
Parathyroidectomy (in cases of severe secondary or tertiary hyperparathyroidism)
Broad-spectrum antibiotics (ulcerating disease with signs of inflammation)
Professional interdisciplinary wound treatment
Potential approaches:
Withdrawal of vitamin K antagonist treatment (switch to heparin or platelet aggregation inhibitors depending on indication)
Cinacalcet (in cases of secondary or tertiary hyperparathyroidism and contraindications against parathyroidectomy)
Bisphosphonates (caution: only if adynamic bone disease can be excluded)
Sodium thiosulfate
Hyperbaric oxygen therapy
Approaches under evaluation:
High-dose vitamin K substitution?
Fetuin-A induction by anti-inflammatory agents?

Calciphylaxis registries

There is no doubt that current data on incidence, pathophysiology, diagnostic and therapeutic strategies on calciphylaxis is insufficient. This situation was considered by the „*Kidney Disease – Improving Global Outcomes*" (KDIGO) initiative, a global and independent non-profit organization, aiming at improvements of the general prognosis of all CKD-associated outcomes. KDIGO developed the concept of prospectively collecting as many calciphylaxis cases as possible to improve understanding of the epidemiology of this syndrome and to collect samples (serum, DNA, biopsy tissues etc.) for evaluation of novel pathomechanisms and risk factors and for setting up data and tissue banking. For these purposes, calciphylaxis registries have been founded in the United Kingdom (Manchester) and Germany (Aachen/Coburg) representing the initial stage of an „*International Collaborative Calciphylaxis Network* (ICCN). The German part of this registry started collecting patients via a web-based online form in October 2006 and has since accumulated data and samples from 43 patients. A

preliminary analysis of this data set revealed that 42% of the cases were associated with warfarin use and that there was no relationship to PTH serum levels. The internet pages are currently solely in German, but can be reached by entering the following URLs: www.calciphylaxie-register.ukaachen.de (active), www.calciphylaxie-register.klinikum-coburg.de (active) and www.calciphylaxie.de (from August 2008). Once such registries are more widely recognized, they may represent the basis for future prospective treatment trials.

Conclusions

Calciphylaxis is a rare, but desastrous complication in the course of chronic kidney disease, associated with extremely high mortality and possibly occurring with increasing incidence. In general, treatment aims at lowering the calcium x phosphorous product. In some cases with clinically significant HPT, parathyroidectomy must be considered. Treatment with vitamin K antagonists should be discontinued and replaced by heparin. Novel scientific insights point to a pathophysiological role of deficiencies of calcification inhibitors (MGP, Fetuin-A) in the induction and manifestation of calciphylaxis.
New potential therapeutic strategies including vitamin K supplementation, calcimimetics, bisphosphonates and sodium thiosulfate may find their way into clinical practice in the future, presently however, they must be considered with appropriate caution in individual cases. Information obtained by calciphylxis registries will hopefully contribute to improvements in outcomes of this deleterious syndrome.

Conflict of interest statement. None declared.

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