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REVIEW

Management of patients with calciphylaxis: current perspectives

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Video abstract

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Abstract: Calciphylaxis (CP) is a rare disorder presenting with painful ischemic skin ulcerations. Its association with end-stage renal disease, but also non-uremic cases have been described. Several risk factors, like metabolic syndrome, calcium-phosphate imbalance, anticoagulative medication and female gender have been discussed. Multidisciplinary therapeutic approaches are necessary since evidence-based guidelines are missing due to lack of pathophysiological understanding of the disease and the absence of studies with large patient cohorts. However, strategies for local wound therapy, reduction of risk factors and systemic therapies are being developed. Changes in duration, frequency and method of hemodialysis and specific medication to lower the calcium upload can be effective in uremic CP cases. Systemic treatments with cinacalcet, sodium thiosulfate or bisphosphonates have been applied successfully in CP patients, but large placebo-controlled randomized trials are still needed to gather better insight into this fatal disease.

Keywords: calciphylaxis, calcific uremic arteriolopathy, non-uremic calciphylaxis, calcification, treatment, sodium thiosulfate

Calciphylaxis (CP) is a rare vasculopathic disorder associated with necrotic skin ulcers and high mortality due to calcification of small cutaneous vessels. It has to be discussed as differential diagnosis when unusual and recalcitrant chronic wounds appear. Since the exact pathogenesis remains unclear, different entities might be subsumed under the term CP. Well known is the synonym calcific uremic arteriolopathy (CUA) when the typical necrotic ulcers appear together with end-stage renal disease, a frequent observed co-morbidity. Around 1% of patients depending on hemodialysis suffer from CUA.[1] Most of the studies dealing with CP were performed in patients with CUA. Typically, in the histological analysis of a deep scalpel biopsy with skin and subcutaneous tissue one can find the trias of calcification of the media layer of small cutaneous vessels, intimal hyperplasia/fibrosis and thrombotic occlusion. The stenosis and occlusion of small dermal and pannicular arterioles leads to the typical clinical presentation of a skin infarction.[2] Additional stainings like van Kossa might help to confirm the calcium deposits.[3] But on the other hand, one can also find lesions with the typical histological pattern without the abovementioned associated renal disease. These cases are described as non-uremic CP and are even harder to verify and to treat.[4] However, the serum calcium and phosphate levels can be affected by a large number of possible underlying disorders beyond chronic kidney disease and these have to be clarified. Among

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these disorders are hyperparathyroidism, tumors, medication or vitamin imbalances.[2]

For lack of alternative options, treatment options known from CUA are also transferred to non-uremic cases despite their off-label use and missing recommendations for a particular therapeutic approach. The systemic therapies and the local wound management for CP will be discussed below. The high mortality described for CUA patients is the impetus for an early diagnosis and treatment. In a case-control study, a 1-year survival rate of 45% was found for CP patients.[5] A monocentric retrospective study in Spain showed a mortality rate higher in CUA than in non-uremic cases of CP.[6] It has been observed that the risk for death is eightfold higher in patients with CP and associated end-stage renal disease compared to other hemodialysis patients.[7]

Diagnosis

CP is considered when necrotic ulcers with surrounding livedo racemosa or indurated plaques occur – particularly in the lower extremities – and additionally when the patient´s history is positive for chronic renal disease or even hemodialysis. However, the presentation of the cutaneous lesions can highly vary concerning their clinical appearance with subcutaneous induration, hemorrhagic patches or stellate-shaped ulcers with thick necrosis as well as the associated comorbidities with likewise described cases of non-uremic CP. An unusual localization can even hinder finding a clear diagnosis.[8]

A review about CP would not be complete without discussion of differential diagnoses, specifically when the association with renal disease as a diagnostic clue is missing. When the ulcers appear on the lower leg, frequent causes of leg ulcer like vascular ulcers have to be clarified. Another important and highly discussed diagnosis with some overlapping patterns to CP is the hypertensive ischemic leg ulcer Martorell.[9] Here, we also find rapidly progressive, painful necrotic ulcers, preferentially on the dorsal calf in association with a history of long-lasting arterial hypertension. Histological findings show also calcification in small cutaneous arterioles. A clear differentiation from CP is often hard to find and some authors postulate a common origin for these ulcers.

Thrombophilic disorders also have to be differentiated when thrombosis of small vessels can be seen in the histological investigation. Livedoid vasculopathy also with painful, necrotic ulcers of the lower leg, livedo racemosa of the surrounding skin and occlusion of small cutaneous vessels can be mentioned as a thrombotic disease which can appear clinically like ulcers from CP.[10] Some authors advocate strict anticoagulative therapy for patients with CP, but the choice of anticoagulative agent is highly restricted since warfarin has been implicated in the pathogenesis of CP as described below.[11] Other causes of cutaneous vessel occlusion like cholesterin embolization, cryoglobulinemia or medication-induced ulcerations have to be differentiated, too.[12] In a case-control study of CP patients with concomitant renal disease, the authors found higher rates of hypercoagulability in the CP patients than in controls with same stages of renal diseases.[13]

To differentiate other underlying diseases with the presentation of skin ulcers parameter for collagenoses or vasculitis, as well as cryoglobulines and antiphospholipid antibodies should be controlled.[12] Taken together, there is some hint of a correlation between CP and hypercoagulability.[14]

Calcium-phosphate levels, stage of renal disease, hypercoagulability and exclusion of differential diagnoses can mainly be performed via an orientating blood analysis. More specific markers of calcification can be added when necessary. Table 1 gives an overview of possible blood markers. To confirm the diagnosis of CP, a single elevated parameter (eg, an increased value of calcium-phosphate product) alone is not evidentiary enough.

Risk factors and co-morbidities

A number of risk factors for the development of CP have been described in case-control studies, mainly for patients with end-stage renal disease. But most studies are still limited by small number of patients or selection bias and true causality has not been determined. In most cases, no data about direct affectation of CP by the described co-morbidity are available.[15] Table 2 shows an overview of highly acknowledged risk factors. Next to end-stage renal disease and its co-morbidities like anemia and cardiovascular diseases, associations of CP with diabetes mellitus have been described.[16] Moreover, smaller numbers of reports have been published about possible associations between CP and autoimmune disorders, infectious or alcoholic hepatitis, antiphospholipid syndrome or duration of dialysis.[15] Chronic inflammatory states are discussed as possible risk factors for vascular calcification as TNF-a induces an osteogenic phenotype of human smooth-muscle cells in vitro.[17] Other cytokines are also linked to calcification. Aluminum excess has also been discussed to be at least a co-factor in the pathogenesis of some CP cases by

Table 1 Recommendations for possible blood analysis in patients with suspicion of CP. The values marked with * might be restricted to cases with further research interest

Parameter	Comment
Creatinine, serum calcium (total), free (ionized) calcium, phosphate, albumine, parathyreoid hormone, calcium- phosphate product, 25-hydroxyvitamin-D, 1-25-dihydroxyvitamin-D	To exclude/confirm (status of known) renal disease or hyperparathyroidism
Alphafetoin*	Glycoprotein of the liver, inhibiting accumulation of hydroxyapatit formations
Serum cystatin C*	Marker of renal function in early acute renal disease
Osteoprotegerin*, GLA-1 (globular arrest 1) protein*, fibroblast growth factor 23*	Paracrine signal proteins involved in vascular calcification
Standard blood coagulation tests, homocysteine, antiphospholipid antibodies	To exclude coagulation disorders
Antinuclear antibodies, antineutrophilic cytoplasmic antibodies	To exclude collagenoses or vasculitis

involvement in the NFkB pathway which itself might influence vascular calcification.[2]

Special emphasis has been placed on the discussion about induction of CP by drugs.[18] Patients with end-stage renal disease are often under multiple medications and should be subject to an explicit review of drugs possibly contributing to CP. Warfarin is one of the best known factors associated with CP and the course of disease. It has been shown that warfarin can negatively influence vitamin K-dependent proteins which prevent vascular calcification. Although this could be shown in animal models, the role of warfarin in human vascular calcification remains unclear.[19] Some authors even postulated distinguishing between warfarin-associated and -unassociated CP.[20] To explore the effect of vitamin K supplementation in patients with uremic CP, a randomized controlled study trial is currently recruiting (ClinicalTrials.gov Identifier: NCT02278692). However, the identification and treatment of underlying coagulative disorders in any case of CP is essential.[21] Stopping warfarin, vitamin D, calcium supplements and iron intake is recommended by the majority when treating CP patients.[18,22,23] Direct thrombin inhibitors have been shown to be safe and well tolerated in smaller case series and lead to improvement of CP.[24] Another case series with 15 patients observed a positive effect for tissue plasminogen activator as an adjunctive treatment option in CP.[25,26] However, these therapeutic decisions require an interdisciplinary approach regarding the individual patient and his underlying morbidities.

Table 2 Overview of risk factors observed for development of CP (data from[5,7])

Chronic kidney disease, hemodialysis, kidney transplant recipient
Hyperphosphatemia
Hypercalcemia
High levels of alkaline-phosphatase Calcium-phosphate product >70 mg^2/dL^2
Secondary hyperparathyroidism
Female gender
BMI >30 kg/m^2
Liver disease
Systemic corticosteroid use
Hypalbuminemia
Warfarin therapy
Serum aluminium >25 ng/mL

Treatment

Clear therapeutic guidelines for the treatment of CP are still missing which is caused by the missing insights into CP pathophysiology so far. Efficient therapeutic procedures and evidence-based recommendations are needed especially for non-uremic CP, since therapeutic strategies can so far only be transferred from CUA treatment without a pathophysiological correlation.[27]

Concepts of a modern wound management should be followed with special emphasis on debridement and prevention or early treatment of wound infections which are involved in the high mortality of CP patients due to sepsis. Non-adhesive modern wound dressings or products with silicone layer can be applied to the wound to enable an

atraumatic dressing change and reduce pain. Antiseptics like octenidin, polihexanide or hypochloric acids as well as antimicrobial effective substances are part of the local treatment regimens. Removal of necrosis and wound debris is essential but often hard to implement due to pain or the patient´s multimorbidity. While some authors advocate an early, consequent surgical debridement,[9] others prefer less invasive treatment like maggot therapy.[28] Debridement can also be combined with negative pressure wound therapy and – after achieving a satisfying granulation tissue – split skin grafting.[29] In a retrospective study of 64 patients, an estimated 1-year survival rate of 61.6% was observed for 17 patients receiving surgical debridement compared with 27.4% for the 46 who did not (p=0.008).[5] However, there is even discussion whether performing deep skin biopsy may worsen the clinical course[30,31] and too intensive manipulation is not advised.[1]

Hyperbaric oxygen therapy (HBOT) might be an adjunctive topical treatment option, but is only available in a small number of specialised centres. In a retrospective analysis of 34 patients with uremic CP, HBOT was very effective with 50% complete wound healing and 58% improvement.[32] Patients have to be selected according to availability and their overall health condition for such specific and extensive local wound treatments.

In addition to modern wound management, a supportive analgesic medication is essential for CP patients. The course of disease is often prolonged or chronic and pain is a frequent symptom which has to be addressed according to its characteristics and specificity with adequate medication according to the analgesic ladder and the patient´s needs.

In summary, local wound therapy in CP patients has to be performed in a professional manner and where available in specialized wound care centers.[33] A clear therapeutic recommendation beyond intensive and antimicrobial local wound care cannot be given according to the currently available literature. Individual therapeutic decisions have to be made and an evaluation by experienced wound carers has to be ensured.

Systemic treatment

While the cessation of warfarin medication and vitamin D or calcium intake has already been discussed above, therapeutic approaches with systemic medication shall be addressed in the following section. As the presented therapeutic strategies mainly derive from those for uremic CP, more efficient therapeutic measures and evidence-based recommendations are needed for non-uremic cases.[27] A clear diagnostic classification as CP is mandatory.

Searching for clinical trials in CP patients does not reveal many hits in research databases. Due to the multimorbidity and limited mobility of CP patients, randomized controlled trials in specialized centers are highly restricted in terms of patient acquisition.[1]

Systematic data collection might be supported by clinical registers like the German Calciphylaxis Network (www.calciphylaxis.net) (NCT02635373).[34]

In CP patients with hemodialysis, the calcium-phosphate product might be positively influenced by changes in frequency, duration or method of blood filtration. Additionally, vitamin D intake or calcium supplements have to be restricted. In a small pilot study, four dialysis patients with CP were successfully treated with lanthanum carbonate, a calcium-free phosphate binder inhibiting the intestinal absorption of phosphate.[35] Results from the EVOLVE trial showed that patients with end-stage renal disease and uncontrolled hyperparathyroidism, a risk factor for CP, showed a lowered incidence of CP over an observation period of 5 years when treated with cinacalcet, a calcimimetic substance activating the calcium-sensing receptor and thereby reducing parathyroid hormone production.[36] Parathyroidectomy is also discussed as a treatment option for patients with CP and secondary hyperparathyroidism.[37] Early treatment is recommended for these cases.[38] However in a comprehensive review, the use of cinacalcet showed a reduction of parathyroid hormone within a period of 1–2 years,[39] so some authors only recommend parathyroidectomy in cases with no response to medication with cinacalcet.[12] A new substance (SNF472) to inhibit progressive calcification in patients with hemodialysis may be promising and future study results have to be awaited to assess its efficacy in CP patients (NCT02790073). The substance inhibits the development of ectopic calcification by blocking the formation and growth of hydroxyapatite crystal.[40] When it comes to treatments focusing on inhibition of calcification, bisphosphonates were also successfully applied in CP patients with and without renal diseases. While the use of bisphosphonates in patients with severe renal disease is usually avoided due to long-term adverse events concerning bone-turnover effects, their effect in a potentially life-threatening disease like CP is promising. Newly proposed pathways discuss the influence of bisphosphonates on different calcification pathways like enhancing osteoprotegerin, inhibiting calcification of vascular smooth-muscle cells or the formation of calcium-phosphate crystals.[41] Even anti-inflammatory effects

are discussed.[41] Several case series showed successful use of bisphosphonates also in non-uremic CP patients.[42,43]

Another approach with a growing number of reported cases of successful treatment is the intravenous use of sodium thiosulfate (STS) in CP patients. The proposed mechanism behind this therapy is its ability to enhance the solubility of calcium in deposits and therefore its availability for dialysis.[41] Other effects may be antioxidative or vasodilatory.[31] Currently, two clinical studies dealing with STS are recruiting in France and the United States. One multicentre, Phase III, randomized placebo-controlled study is focusing on the potential of STS to reduce pain in CP patients (NCT03150420) next to the clinical improvement of skin lesions while another retrospective follow-up study comprises one of the largest global cohorts of CP patients treated with STS and investigates the influence of STS on patients´ mortality. More than 350 cases with the use of STS in CP patients have been reported so far,[44] either with STS alone or as part of a combination therapy. Positive effects were seen in CP patients with renal disease/dialysis[45] as well as in non-uremic CP cases[46] where the therapeutic effect cannot be explained so far. Even intralesional injections have been described occasionally[47] and showed a good clinical improvement but pain during injections. Due to the renal clearance of STS, dosages and application frequency for intravenous application have to be adapted to renal function and the presence of dialysis. Specific side effects are rare and can be handled by supportive therapy.[41] Table 3

Table 3 Therapeutic options for the treatment of CP

Local wound therapy	
Debridement	Adapted to extent of necrosis, wound surface area, pain and available method
Modern wound dressings	To maintain atraumatic wound dressing
Antiseptic and antimicrobial effective wound dressings	For prevention or therapy of wound infection
HBOT	Adapted to availability
Systemic (supportive) therapy	
Pain medication	Adapted to degree of pain and individual patient´s requirement
Antibiotics	For therapy of wound infection
Cessation of vitamin K-antagonists	Supplement of vitamin K can be considered
Anticoagulation with direct thrombin inhibitors or tissue plasminogen activator	Especially if clues for underlying coagulative disorder can be found.
Systemic therapy (in case of calcium overload)	
Optimization of the underlying renal disease	
Changes in frequency or duration of dialysis, change of filtration/dialysis system	
Calcium-free phosphate binders	
Reduction of vitamin D intake	
Cinacalcet	When secondary hyperparathyroidism is confirmed
Parathyreoidectomy	When hyperparathyroidism is confirmed
Systemic therapy to reduce calcification	
Sodium thiosulfate	Adapted to renal disease or dialysis
Bisphosphonates SNF472	Attention should be paid to possible side effects or contraindications So far only in study protocols

Abbreviation: HBOT, hyperbaric oxygen therapy.

Table 4 Overview of recruiting studies worldwide (data survey on clinicaltrials.gov on 05/06/2019)

ClinicalTrials.gov identifier	Title	Study type	Study design	Study substance
NCT03150420	A Phase 3 Clinical Trial of Intravenous Sodium Thiosulfate in Acute Calciphylaxis Patients (CALISTA)	Interventional	• Multicentre • Randomized • Double-blind • Placebo-controlled • 111 patients planned	Sodium thiosulfate
NCT02278692	Evaluation of Vitamin K Supplementation for Calcific Uremic Arteriolopathy (VitK-CUA)	Interventional	• Single center • Randomized • Placebo-controlled • 20 patients planned	Vitamin K
NCT02635373	European Calciphylaxis Registry Network (EuCalNet)	Observational	• Prospective • Registry • 1000 patients planned	N.A.
NCT03032835		Observational	• Prospective • Registry • 300 patients planned • Observation for 20 years	N.A.

summarizes therapeutic attempts made in CP patients while Table 4 gives an overview of currently recruiting clinical studies.

Conclusion

The diagnosis of CP is often obvious with the typical necrotic ulcers and a history of chronic renal disease or dialysis. Several risk factors have been identified and should be addressed early in affected patients. Different treatment approaches for local and systemic therapy have been acknowledged although randomized controlled studies are still missing. Next to an atraumatic and antiseptic wound management, systemic approaches like improvement of calcium and phosphate levels as well as treatment of secondary hyperparathyroidisms are among the therapeutic considerations. The systemic application of STS or bisphosphonates is confirmed as successful in several case studies. Randomized controlled studies on larger cohorts are needed to clear upcoming issues about dosage, treatment duration and long-term outcomes. Diagnosis and treatment are hindered for the non-uremic forms of CP where so far the concepts of CUA can only be transferred in lack of distinct recommendations.

Disclosure

The authors report no conflicts of interest in this work.

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