

## Calcific arteriopathy (calciphylaxis). Recommendations for its management

*Arteriopatía calcificante (calcifilaxis). Recomendaciones para su manejo*

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Calcific arteriopathy (uremic or non-uremic) or calciphylaxis is a disease of low prevalence and high morbidity and mortality (orphan disease: orphanet number ORPHA280062) associated with vascular calcification (calcium deposition in the arteriolar tunica media), and propitiates the formation of microthrombi, with the consequent generation of distal ischemia and subcutaneous necrosis<sup>1,2</sup>. The infection of these ischemic lesions (necrotic ulcers) leads to sepsis, which is the main cause of death in these patients<sup>1</sup>.

Calcific arteriopathy most frequently affects patients with advanced chronic nephropathy (calcific uremic arteriopathy), although it should be noted that most of the extraskelatal calcifications of these patients are not calciphylaxis; as well as the fact that not all cases of calcific arteriopathy occur in renal patients (acute or chronic), but it has been reported even in patients with normal renal function (non-uremic calcific arteriopathy), in the context of oncological diseases or the use of certain drugs<sup>1,2</sup>.

Given the seriousness of this entity, and the importance of the universalization of the knowledge thereof by the nephrology community, we present below an updated summary of the main recommendations for its diagnosis and treatment<sup>2-10</sup>.

- Since it is an entity that is usually underdiagnosed or diagnosed late, attention should be paid and a high degree of suspicion should be maintained in the presence of any cutaneous symptom or sign presented by the nephrological patient. The early lesion (pre-ulcerous) is usually spontaneously painful, hyperesthetic and indurated to the touch (plaque or nodule), and generally accompanied by livedo or purpura. Its differential diagnoses, for whose definition contributes the cutaneous biopsy, should be taken into account (Table 1). Although it has been proposed not to perform it when it comes to typical lesions in patients on chronic dialysis, due to its potential risks of superinfection and/or appearance of new lesions, it must be borne in mind that most of the dermatoses that constitute a differential diagnosis with calciphylaxis (and that on the other hand have a treatment different of this one), are precisely more prevalent in patients with nephropathies (Table 1).
- Regarding the skin biopsy, it should reach the hypodermis and its technique must be adapted to the type and location of the lesion. It is recommended to biopsy the margin of the active lesions, avoiding central lesions or necrotic areas. The tissue obtained should be studied histopathologically including the staining for calcium (von Kossa), the search of parasites and the culture for bacteria and fungi.
- Although the most frequent manifestation of calciphylaxis is cutaneous, it should be remembered that the condition can also manifest itself as ischemia of other organs, standing out its appearance in muscle (myopathy), digestive tract (digestive hemorrhage) and eyes (visual alterations).

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**Table 1.** Differential diagnoses of calciphylaxis.

Dermatopathy	Higher prevalence in nephropathy
Warfarin-induced skin necrosis	Yes (anticoagulation)
Ischemic atherosclerotic arterial ulcer	Yes (hypertension and diabetes mellitus)
Metastatic calcinosis cutis	Yes (altered phosphorus-calcium metabolism)
Dystrophic calcinosis cutis	Yes (autoimmunity, chronic inflammation)
Mönckeberg's arteriosclerosis	Yes (hypertension and diabetes mellitus)
Venous stasis ulcer	No
Bacterial, fungal or parasitic cellulitis	Yes (immunosuppression)
Atheroembolism	Yes (endovascular procedures)
Livedoid vasculopathy	Yes (autoimmunity)
Oxalosis	Yes (oxalate nephropathy)
Gangrenous pyoderma	No
Disseminated intravascular coagulation	Yes (immunosuppression - sepsis)
Purpura fulminans	No
Nephrogenic systemic fibrosis	Yes (gadolinium)

- The management of these patients must be interdisciplinary, integrating the actions of the nephrologist, the dermatologist, the pain specialist, the nutritionist, and the plastic surgeon, among others.
- The elevation of serum levels of calcium and phosphate increases the risk of calciphylaxis in patients under dialysis treatment; therefore, it is important to attempt to maintain these levels within normal values. However, it has been reported that 86 % and 40 % of patients with calciphylaxis on chronic dialysis have normal-low calcemia and phosphatemia, respectively. The optimal serum level of parathyroid hormone in this entity is unknown, but extreme values (high or low) should be avoided. The intake of oral calcium, vitamin D (in whichever form) and dialysate bath rich in calcium should be avoided. Given the risk of appearance of the «hungry bone syndrome» associated with the post-operative period of parathyroidectomy, with its requirement of high calcium and calcitriol intake, it is preferable to try to resolve the hyperparathyroidism initially with calcimimetics.
- The use of warfarin (vitamin K antagonist) increases the risk of calciphylaxis, and even vitamin K deficiency (malabsorption, etc.) is observed in 80 % of patients with chronic nephropathy with calciphylaxis. If is required to start an anticoagulant treatment, a valid alternative might be to opt for the new oral anticoagulants.
- The application of subcutaneous (or intramuscular) injections should be avoided and, if this is not possible, the puncture area should be alternated.
- As there is no validated treatment for the calcific uremic arteriolopathy, randomized studies including a sufficient number of patients are required, with which it would be possible to obtain Results with statistical significance.

In [Table 2](#), we summarize the different therapeutic strategies proposed to date. Finally, in order to increase the knowledge of this entity and to contribute to its effective treatment, we invite all colleagues interested in the subject to join the Colombian Registry of Calciphylaxis of the Colombian Association of Nephrology, which works through its NEFRORED platform.

**Table 2.** Reported treatments for calciphylaxis (diverse degrees of evidence).

Proposed treatments	Objective
Sodium thiosulfate (endovenous #, oral, local).	Specific treatment
Bisphosphonate (endovenous)	Specific treatment
Hyperbaric chamber #	Specific treatment
Calcimimetics (cinacalcet)	Specific treatment
Parathyroidectomy	Specific treatment
Aprostadil (combined with #)	Specific treatment
Kidney transplant	Specific treatment
Rheopheresis (hypothesis)	Specific treatment
Vitamin K (if there is deficiency or use of warfarin) (oral)	General measure
Remove necrotic tissue	General measure
Protein-calorie nutrition	General measure
High dose dialysis (daily dialysis to remove phosphates)	General measure
Gabapentin, ketamine	Analgesia

## Conclusion

Calcific arteriopathy is an entity of low prevalence, but of high risk in the patient with end stage chronic renal insufficiency, up to now, its main therapeutic strategy is to reduce, as far as possible, its risk factors and achieve early diagnosis in order to try to improve its evolution and prognosis.

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