Clinical Kidney Journal, 2022, vol. 0, no. 0, 1–4

https://doi.org/10.1093/ckj/sfab247
Advance Access Publication Date: 15 December 2021
Editorial Comment

EDITORIAL COMMENT

Calciphylaxis after kidney transplantation: a rare but life-threatening disorder

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ABSTRACT

Calciphylaxis is a rare disorder characterized by vascular calcification and thrombosis of the subcutaneous microcirculation, leading to painful necrotic skin lesions and bearing a dreadfully high mortality rate. This syndrome is frequently also termed uraemic calcific arteriolopathy, since most cases are observed in patients with kidney failure. However, it is increasingly clear that calciphylaxis may also affect patients with normal or only slightly impaired renal function, including kidney transplant recipients. A precise definition of the characteristics and risk factors of calciphylaxis developing after kidney transplantation has been hindered by the extreme rarity of this condition, which also hampered the development of effective therapeutic strategies. In the present issue of *CKJ*, Guillén and colleagues report the largest case series of calciphylaxis in kidney transplant recipients to date, outlining several features that are apparently specific to this population. In this editorial, we briefly present the epidemiology and pathogenesis of calciphylaxis in different patient populations and discuss recent findings for its therapeutic management.

Keywords: calcific uraemic arteriolopathy, chronic kidney disease, renal transplantation, vascular calcification

SCOPE OF THE PROBLEM

Calciphylaxis is an extremely rare syndrome characterized by vascular calcification and thrombosis of the subcutaneous microcirculation. Ensuing ischaemia results in multiple painful skin lesions, which rapidly progress to ulceration with black eschars once necrosis of epidermal and adipose tissue has developed [1]. Short-term prognosis is poor, usually due to superimposed infections resulting in sepsis [2–4].

Since calciphylaxis is typically observed in patients with kidney failure, this syndrome is frequently also termed uraemic calcific arteriolopathy [2, 3, 5]. Chronic kidney disease is associated with progressive vascular calcification, and uraemia leads to extensive alterations in bone mineral handling that may predispose to calciphylaxis. However, several case series have clarified that calciphylaxis may also seldom affect patients with normal or only slightly impaired renal function, including kidney transplant recipients [3, 6].

Large national databases have allowed a systematic assessment of calciphylaxis features in patients with kidney failure on renal replacement therapy. The incidence rate of calciphylaxis has been estimated at 0.4–3.5 per 1000 patients/year in US and European haemodialysis units [2, 3, 7], whereas the incidence may be higher for patients on peritoneal dialysis (Table 1) [8].

These studies identified relevant risk factors in this population, which comprise female sex, obesity, diabetes mellitus, hyperparathyroidism and length of dialysis vintage. In addition,

Received: 24.11.2021; Editorial decision: 2.12.2021

Table 1. Clinical features of calciphylaxis in haemodialysis patients, peritoneal dialysis patients and kidney transplant recipients

	Haemodialysis [2, 3]	Peritoneal dialysis [8]	Kidney transplant [9]	Non-uraemic [6]
Incidence (per 1000 patient/years)	0.4–3.5	9.0	–	–
Median age (years)	54–70	50	44	60
Females (%)	63–67	71	48	77
Central lesions (%)	82	–	36	61
VKA use (%)	14–51	71	39	47
Diabetes mellitus (%)	55–61	43	23	32
Altered PTH levels (%)	–	57	75	25
Mortality	45–80% at 1 year	71% at 1 year	56% overall	Median survival: 4.2 months

VKA, vitamin K antagonists; PTH, parathormone.

several medications have been identified as possible facilitators of calciphylaxis development, including oral anticoagulants based on vitamin K antagonism [2, 8, 10]. However, due to the extreme rarity of this disease in non-uraemic patients, a comparatively large case series of kidney transplant recipients is not available.

MULTIFACTORIAL PATHOGENESIS

Vascular calcification in chronic kidney disease does not entail a merely passive deposition of hydroxyapatite crystals in arterial walls, but is rather an actively regulated process in which pro-calcifying stimuli outbalance the protective effect of calcification inhibitors [11]. These alterations induce trans-differentiation of vascular smooth muscle cells towards an osteochondrogenic phenotype, which results in arterial remodelling and mineralization. In uraemic patients, calcium–phosphate imbalances, oxidative stress and comorbidities (e.g. diabetes mellitus and hypertension) concur in causing vascular calcification [12].

Despite the resolution of uraemia after kidney transplantation, vascular calcification may still develop and progress in these patients due to the effect of other risk factors, such as inflammation, immunosuppression and calcification inhibitor deficit [13]. The latter seems to be pivotal in the pathogenesis of calciphylaxis, with several studies suggesting a role for reduced matrix-Gla protein (MGP) and fetuin-A levels. MGP is a calcium-chelating protein and a potent inhibitor of vascular smooth muscle cell trans-differentiation, the activation of which relies on vitamin K-dependent carboxylation [14]. Vitamin K deficit, a common occurrence in both uraemic patients and kidney transplant recipients, is associated with high levels of uncarboxylated—i.e. inactivated—MGP, which represents an independent predictor of vascular calcification [15]. High levels of uncarboxylated MGP have been reported in skin biopsies and in the serum of patients with calciphylaxis, and have been associated with vitamin K deficiency [16, 17]. This may in part explain the association of vitamin K antagonist use and the development of calciphylaxis in uraemic patients. Similarly, low levels of fetuin-A, a circulating glycoprotein that complexes amorphous phosphate, have been reported in patients with calciphylaxis [18]. Thrombosis of the microcirculation has been increasingly recognized as a crucial precipitative factor in the development of calciphylaxis, which frequently ensues as a consequence of traumatic events. Interestingly, a hypercoagulable state seems to be highly prevalent in these patients [19], providing a possible explanation for the rarity of this condition.

CALCIPHYLAXIS IN KIDNEY TRANSPLANT RECIPIENTS

In the present issue of *CKJ*, Guillén and colleagues report the largest case series of calciphylaxis in kidney transplant recipients to date, obtained from a monocentric retrospective data search spanning over 30 years [9]. The authors also conducted a systematic review of cases published in international literature during the last 50 years, adding up to a total of 45 patients, to provide a meaningful description of disease features in this population.

A significant proportion of kidney transplant recipients who developed calciphylaxis had moderate graft dysfunction and a relatively long dialysis vintage (median 24 months), along with a past history of graft failure that led to re-transplantation. In addition, calciphylaxis developed during the first year of transplantation in almost half of these patients, suggesting a likely carry-over effect of uraemia-related risk factors.

Calciphylaxis in this cohort had some key differences when compared with features typically observed in patients with kidney failure (Table 1). There was no female predominance, with a roughly even frequency of males and females, and only one-quarter of patients had diabetes. In addition, lesions distribution was mostly peripheral, contrasting with the distinct preponderance of central lesions (i.e. involving areas with an abundance of adipose tissue such as abdomen and thighs) observed in haemodialysis patients [2, 3].

Altered parathormone levels were observed in most patients and the study confirmed a high frequency of use of vitamin K antagonists in kidney transplant recipients with calciphylaxis, suggesting that vitamin K deficiency may indeed play a significant role also in these patients. Mortality was unfortunately high also in this cohort, with an overall short-term survival of 44%.

To account for changes in the standard of care of kidney transplant recipients over the last three decades, the authors also compared the characteristics of cases diagnosed before and after 2000. Despite differences in immunosuppressive regimens and demographic features (patients diagnosed after 2000 were older and with longer dialysis vintage), most of the other characteristics were comparable between groups.

TREATMENT OPTIONS

Calciphylaxis is a complex syndrome that requires a multidisciplinary approach, including wound care, analgesia and removal of known risk factors. Despite advances in the understanding of calciphylaxis pathogenesis, therapeutic management is still based on expert consensus and there is no currently approved

treatment for this condition [20]. Due to the extreme rarity of calciphylaxis in kidney transplant recipients, virtually all available data on treatment are derived from patients on haemodialysis.

Normalization of calcium–phosphate metabolism is a reasonable first step, along with removal of possible iatrogenic factors, including calcium supplements, vitamin D analogues and vitamin K antagonists [1, 21]. In dialysis patients, longer or more frequent dialysis sessions with low-calcium dialysate may improve metabolic control and enhance wound healing [1, 22]. In patients with severe hyperparathyroidism, the use of calcimimetics or parathyroidectomy could be beneficial [23, 24]. Bisphosphonates have also been successfully used to inhibit the progression of lesions in some patient series [25], but no prospective trials have been conducted to date.

Sodium thiosulphate, an inorganic sodium salt with antioxidant and vasodilator properties, is among the most used agent for calciphylaxis treatment. Retrospective data suggested a good efficacy–safety profile, with most patients improving after administration [26]. Three randomized controlled trials had been planned to prospectively assess the efficacy of sodium thiosulphate (NCT03150420, NCT02527213 and ISRCTN73380053), but they were all terminated early due to insufficient patient enrolment.

Other promising therapeutic alternatives include hyperbaric oxygen therapy to improve transcutaneous oxygen tension, rheopheresis and bosentan to reduce blood viscosity and promote arteriolar vasodilation, and non-vitamin K antagonist anticoagulants to salvage thrombosis of the microcirculation [1, 27].

A recent meta-analysis of case series and cohort studies failed to show any clear benefit on mortality from all the therapies explored, including thiosulphate, parathiroidectomy, cinacalcet, hyperbaric oxygen therapy and bisphosphonates [28]. However, the quality of evidence was low and results were inconclusive, reflecting the lack of randomized controlled trials that explored the effect of these treatments.

Increasing MGP carboxylation through vitamin K supplementation has been proposed as a possible additional therapeutic strategy for calciphylaxis. Preliminary results from a phase II trial (NCT02278692) comparing vitamin K1 with placebo in haemodialysis patients suggested a relevant clinical efficacy, with a benefit on both lesion size and mortality at 12 weeks [29].

Finally, the use of SNF472, a polyphosphate compound that inhibits hydroxyapatite crystal formation, has been explored recently in a phase 2, single-arm, open-label study on 14 haemodialysis patients with calciphylaxis. Treatment was well tolerated and led to improvements in wound size, pain and quality of life at 12 weeks [30]. A phase 3 randomized clinical trial has been planned to evaluate the efficacy of SNF472 with a placebo [31].

CONFLICT OF INTEREST STATEMENT

None declared.

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