Development of calciphylaxis in kidney transplant recipients with a functioning graft

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ABSTRACT

Background. Calciphylaxis is not uniquely observed in uraemic patients, as some cases have also been reported in patients with normal renal function or moderate chronic kidney disease (CKD), in association with severe vasculopathy or systemic inflammation. A particular subset worthy of studying is represented by those patients who develop calciphylaxis after kidney transplantation (KT).

Methods. Analysis of the local series of calciphylaxis after KT (n = 14) along with all the other cases reported in the literature from 1969 to 2019 (n = 31), for a total population of 45 patients, is presented. Demographic data, CKD history, risk factors, immunosuppression, clinical presentation and management have been analysed both as a whole and according to the time period (before or after the year 2000).

Results. Calciphylaxis developed during the first year after KT in 43.2% of patients and median (interquartile range) creatinine at diagnosis was 2.4 (1.25–4.64) mg/dL. The most frequent presentation included distal purpura or ulcers in one-third of cases and 39.1% of patients were receiving vitamin K antagonists. PTH values were above 500 pg/mL and below 100 pg/mL in 50.0% and 25.0% of cases, respectively. Whole population mortality was 55.6%. As expected, clinical presentation, immunosuppression and management varied depending on the time period. Patients diagnosed after 2000 were older, with longer dialysis vintage, and treatment was usually multimodal; on the contrary, in patients diagnosed before 2000, parathyroidectomy was the treatment of choice in 61.9% of cases.

Conclusions. Calciphylaxis can still occur after KT, in many cases during the first year and in patients with a good renal function. Risk factors and management varied according to the time period studied.

Keywords: bisphosphonates, calcific uraemic arteriolopathy, calcification, calcineurin inhibitors, calciphylaxis, cinacalcet, immunosuppression, kidney transplantation, parathyroidectomy, sodium thiosulphate
INTRODUCTION
Calciﬁphyaxis is a clinical syndrome characterized by purpura, nodules or necrotic ulceration as a consequence of the critical calcification of the terminal (candelabra) skin arterioles followed by acute thrombosis. Pathogenesis includes a progressive calcification of the media and ﬁbrosis of the intima that reduce the lumen of the skin vessel. Some clinical events, such as local trauma, hypotension or hypercoagulability, can ﬁnally trigger thrombosis and this leads to the development of clinical manifestations [1]. Many factors participate in this process, including classical Framingham risk factors, uremia, altered mineral metabolism, vitamin K inhibitors, chronic inﬂammation and demographic characteristics. These factors often co-exist in end-stage renal disease (ESRD) patients, which is the typical clinical setting in which calciﬁphyaxis is observed. For this reason, it is also known as calciﬁc uremic arteriolopathy (CUA) [2]. However, it may occur also in patients without ESRD, i.e. in patients with chronic kidney disease (CKD) not on dialysis and in patients with a normal renal function but with severe vasculopathy and/or chronic inﬂammatory conditions [3, 4]. A speciﬁc subset is represented by those patients with a long history of CKD and vasculopathy who regain renal function after kidney transplantation (KT). In this setting, even though the transplanted kidney should improve the vasculopathy by restoring the mineral balance, the long-standing vascular risk factors and, possibly, some immunosuppressive drugs may continue the calciﬁcation process of the small arterioles [5]. The ﬁrst such case in KT was reported in 1969 [6] and since then other reports have added substantial knowledge to the behaviour of calciﬁphyaxis in this very speciﬁc setting. However, the reported cases are heterogeneous and cover a wide period, from the early era of KT to present [6–30]. This implies that risk factors, patients’ characteristics and treatment modalities have changed across time and few certainties can be drawn so far. We present herein our experience of 14 cases, which, to our knowledge, is the largest series of calciﬁphyaxis reported in KT. We analysed these data along with the other 31 reported cases in the literature in order to study the characteristics of calciﬁphyaxis in such an unusual context.

MATERIALS AND METHODS
The authors searched PubMed using the Medical Subject Headings (MeSH) terms (calciﬁphyaxis AND kidney transplant OR kidney transplant) in all papers published from 1969 to date, either written in English or not. Cases included were those with clinical and/or histological diagnosis of calciﬁphyaxis that occurred after KT in a still-functioning graft. The full text of these articles were revised and data were collected about age, gender, ethnicity, comorbidities, time of evolution of ESRD (dialysis and transplantation vintage), immunosuppression regimen, lesion location and clinical manifestation, laboratory parameters, offered treatments and outcomes.

The local cohort included the cases of calciﬁphyaxis after KT diagnosed at the Hospital Clinic of Barcelona (Spain) from 1990 to 2020. Demography and clinical characteristics were thoroughly reviewed through a case report form, as well as radiological images and biopsies.

Skin biopsies were reviewed by a pathologist specialized in KT and dermatology (A.G.-H). Staining for calcification was performed with the von Kossa method [31]. Imaging with low-energy-X-rays (mammographic technique) was performed adapted to different anatomical regions, due to its accuracy in showing calcifications [1].

RESULTS
Hospital Clinic case reports
We report 14 cases of calciﬁphyaxis after KT diagnosed at our institution until 2020 (Tables 1 and 2). Seven cases were already described in a previous publication of 1998 [15] and no more data were available, apart from those of the original publication. Table 1 shows the analysis of this population as a whole and according to the time period (before or after 2000), while Table 2 provides more precise data on patients diagnosed after 2000. Regarding the latter category of patients, most were females (four of seven cases, 57.1%) with a median age at diagnosis of 65 (52–76) years. One patient (14.3%) had previous history of diabetes mellitus; none was obese; four were undergoing treatment with vitamin K inhibitors (57.1%); and only one patient (14.3%) had a history of previous parathyroidectomy. Dialysis and transplant vintage were 36 (16–228) and 48 (1–53) months, respectively. Immunosuppression was based on calcineurin inhibitors (CNI) either alone or in combination with either mycophenolate (MPA) or mTOR inhibitors (mTORi) in six patients (85.7%). All patients were also carrying prednisone with a dose of 2.5–5 mg daily.

The median value of creatinine at diagnosis was 3.30 (2.80–3.90) mg/dL, serum calcium 9.80 (9.30–10.00) mg/dL and phosphorus 4.50 (3.9–6.0) mg/dL with a Ca × P product of 44.1 (33.9–55.8) mg²/dL². Regarding parathyroid hormone (PTH) levels, median value was 936 (278–1105) pg/mL, with most patients (57.1%) having PTH values > 900 pg/mL, while the patient with previous parathyroidectomy displayed levels of 48 pg/mL.

Given the distribution of the published cases along the years (Figure 1), we analysed the global experience as a whole (local cohort and reported cases), and depending on whether the cases were published before 2000 or not.

Data are presented as numbers and/or percentages, or median and interquartile range, as indicated. Differences between groups were analysed with Mann–Whitney’s and Fisher’s exact test, according to the studied variable (continuous/dichotomous). Statistical analysis was carried out through the software SPSS v.17 (SPSS Inc, Chicago, IL, USA) and GraphPad v.5 (GraphPad Software, La Jolla, CA, USA).
Table 1. Hospital Clinic case reports according to the time period (before and after 2000)

|                        | Whole population (n = 14) | Before 2000 (n = 7) | After 2000 (n = 7) | P-value |
|------------------------|---------------------------|----------------------|--------------------|---------|
| Age (years)            | 53.5 (46.25–68.25)        | 47 (39–62)           | 65 (52–76)         | 0.097   |
| Sex (% males)          | 50.0                      | 57.1                 | 42.9               | 0.952   |
| Diabetes mellitus (% yes) | 14.3                    | 14.3                 | 14.3               | 1       |
| Dialysis vintage (months) | 54 (33–73.5)             | 60 (36–72)           | 36 (16–228)        | 0.620   |
| Transplant vintage (months) | 48 (30–72)              | 66 (45–73.5)         | 48 (1.2–53)        | 0.181   |
| Baseline immunosuppression, % |                       |                      |                    |         |
| CNI                    | 78.6                      | 85.7                 | 71.4               | 0.843   |
| MPS                    | 28.6                      | 0.0                  | 57.1               | 0.070   |
| AZA                    | 14.3                      | 28.6                 | 0.0                | 0.462   |
| mTORi                  | 21.4                      | 0.0                  | 42.9               | 0.192   |
| PDN                    | 100.0                     | 100.0                | 100.0              | 1       |
| Creatinine (mg/dL)     | 3.3 (2.47–6.85)           | 6.6 (2.4–8)          | 3.3 (2.8–3.9)      | 0.456   |
| Calcium × phosphorus (mg²/dl²) | 48.8 (32.65–66.52)     | 64.7 (31.6–70)       | 44.1 (33.9–55.8)   | 0.710   |
| PTH (pg/mL)            | 717 (339–1173)            | 596 (360–1550)       | 936 (278–1105)     | 1       |

Treatment, %
- Thiosulphate: 21.4%
- Parathyroidectomy: 21.4%
- Biphosphonates: 35.7%
- Cinacalcet: 28.6%

Mortality (% yes) 21.4%

Data are presented as median (interquartile range) unless otherwise indicated. PDN, prednisone.

Table 2. Hospital Clinic case reports after 2000

| Patient | Age (years) | Sex | Ethnicity | Diabetes mellitus | Dialysis vintage (months) | Transplant vintage (months) | Previous transplant (number) | Previous parathyroidectomy | Medication | Baseline immunosuppression | Creatinine (mg/dL) | Calcium (mg/dL) | Phosphorus (mg/dL) | PTH (pg/mL) | Lesion location | Clinical manifestation | Histological confirmation | Ferritin (ng/mL) | Transferrin saturation (%) | Treatment | Outcome |
|---------|-------------|-----|-----------|-------------------|--------------------------|----------------------------|----------------------------|------------------------------|------------|-------------------------|------------------|----------------|---------------------|------------|----------------|------------------------|----------------------|----------------|-------------------------|-----------|---------|
| 1       | 52          | Male| Caucasian | No                 | 36                       | 48                         | No                         | No                           | VKI        | PDN + CNI + MPA + mTORi | 3.30             | 9.40           | 4.20                | 936        | Distal         | Necrosis              | Yes                   | n/a              | 19.20                   | Bisphosphonate | Alive  |
| 2       | 76          | Male| Caucasian | No                 | 16                       | 48                         | No                         | No                           | VKI        | PDN + CNI + MPA + mTORi | 2.80             | 8.90           | 4.50                | 1105       | Distal         | Distal                | Yes                   | 56              | 11.40                   | Cinacalcet    | Dead   |
| 3       | 49          | Male| Caucasian | No                 | 612                      | 24                         | No                         | No                           | Statins    | PDN + CNI + mTORi         | 3.30             | 10.70          | 5.00                | 1020       | Distal         | Distal                | Yes                   | 74               | 17                      | Cinacalcet    | Dead   |
| 4       | 67          | Male| Caucasian | No                 | 72                       | 24                         | No                         | No                           | Statins    | PDN + CNI + mTORi         | 3.00             | 10.00          | 6.90                | 48         | Distal         | Distal                | Yes                   | 35              | 24.80                   | Cinacalcet    | Dead   |
| 5       | 65          | Female| Caucasian | Yes                | 24                       | 24                         | No                         | No                           | Statins    | PDN + CNI + mTORi         | 3.30             | 9.00           | 2.70                | 1         | Distal         | Distal                | Yes                   | 51              | 11.70                   | Bisphosphonate | Alive  |
| 6       | 83          | Male | Hispanic  | No                 | 24                       | 1                          | No                         | No                           | Statins    | PDN + CNI + mTORi         | 3.64             | 8.70           | 3.90                | 1378       | Distal         | Distal                | Yes                   | 33              | 18.00                   | Cinacalcet    | Alive  |
| 7       | 52          | Male | Male      | Yes                | 53                       | 1                          | Yes                        | Yes                          | Statins    | PDN + CNI + mTORi         | 3.15             | 8.00           | 3.90                | 157        | Ucer          | Ucer                  | Yes                   | 522             | 778                     | Cinacalcet    | Alive  |

PDN, prednisone; VKI, vitamin K inhibitors.

All patients developed distal lesions at presentation, the majority being ulcers (71.4%). In most cases, a combined treatment was employed that included bisphosphonates, thiosulphate and cinacalcet. Two patients eventually died for complications related to calciphylaxis (mortality of 28.5%).

Whole-population characteristics

We identified 24 articles [6–14, 16–30] that included 31 cases of calciphylaxis after KT diagnosed between 1969 and 2020 (Table 3). Summing up the cases reported by our institution at present and in the previous publication [15], the study population was composed of 45 cases of calciphylaxis after KT (Figure 2). All information was not available and the number of missing values for each clinical variable is displayed in figure legends.

Demographic data. The whole-population median age was 44 (33–59.5) years. Patients diagnosed before 2000 were younger than those diagnosed after 2000 [39 (27–47) versus...
Table 3. Whole population—demographics, ESRD history, immunosuppression scheme, clinical presentation, laboratory findings, calciphylaxis treatment and outcomes

|                                    | Whole population (n = 45) | Before 2000 (n = 21) | After 2000 (n = 24) | P-value |
|------------------------------------|---------------------------|----------------------|---------------------|---------|
| Age (years)                        | 44 (33–59.5)              | 39 (27–47)           | 52 (43.75–67.75)    | 0.001   |
| Sex (% males)                      | 52.3                      | 50.0                 | 54.5                | 1       |
| Dialysis vintage (months)          | 24 (12–72)                | 18 (10–51)           | 30 (13–120)         | 0.059   |
| Transplant vintage (months)        | 20 (4–46)                 | 12.5 (4.75–39)       | 24 (1.87–63.75)     | 0.431   |
| Sum (months)                       | 33 (14.5–122.25)          | 20.25 (12.5–78)      | 73.2 (16–192)       | 0.045   |
| Diabetes mellitus (% yes)          | 23.3                      | 22.2                 | 23.8                | 1       |
| Vitamin K antagonist (% yes)       | 39.1                      | 0.0                  | 42.9                | 0.502   |
| Previous parathyroidectomy (% yes) | 25.0                      | 27.3                 | 23.8                | 1       |
| Immunosuppression (% yes)          | CNI 52.8                  | 33.3                 | 72.2                | 0.044   |
|                                   | MPA 36.1                  | 66.7                 | 5.6                 | <0.001  |
|                                   | AZA 22.2                  | 0.0                  | 44.4                | 0.003   |
|                                   | mTORi 100.0               | 100.0                | 100.0               | 1       |
| Lesion location, %                 | Distal 63.6               | 41.7                 | 76.2                | 0.067   |
|                                   | Proximal 36.4             | 58.3                 | 23.8                |         |
| Clinical manifestations, %         | Purpura 33.3              | 58.3                 | 19.0                | 0.090   |
|                                   | Ulcers 33.3               | 25.0                 | 38.1                |         |
|                                   | Necrosis 18.2             | 16.7                 | 19.0                |         |
|                                   | Nodules 15.2              | 0.0                  | 23.8                |         |
| Laboratory values at diagnosis     | Creatinine (mg/dL)        | 2.4 (1.25–4.64)      | 2.4 (1.3–6.6)       | 0.735   |
|                                   | Total calcium (mg/dL)     | 9.8 (9.1–10.5)       | 10.25 (9.42–10.72)  | 0.020   |
|                                   | Phosphate (mg/dL)         | 4.04 (3.10–4.75)     | 3.55 (3–4.2)        | 0.077   |
|                                   | Calcium × phosphate (mg^2/dL^2) | 37.8 (29.28–54.29) | 36.54 (28.87–55.48) | 0.824   |
|                                   | PTH (pg/mL)               | 514 (125–1083)       | 838 (309–1200)      | 408 (48–1020) | 0.212   |
|                                   | -100, %                   | 25.0                 | 15.4                | 31.6    | 0.525   |
|                                   | 100–500, %                | 25.0                 | 23.1                | 26.3    |         |
|                                   | >500, %                   | 50.0                 | 61.5                | 42.1    |         |
| Histological confirmation (% yes) | 68.4                      | 56.3                 | 77.3                |         |
| Treatment, %                      | Pentoxifilline            | 8.3                  | 0.0                 | 15.8    | 0.231   |
|                                   | Thiosulphate              | 22.2                 | 0.0                 | 42.1    | 0.003   |
|                                   | Parathyroidectomy         | 37.5                 | 61.9                | 10.5    | 0.001   |
|                                   | Biphosphonates            | 22.2                 | 5.9                 | 36.8    | 0.044   |
|                                   | Cinacalcet                | 16.7                 | 0.0                 | 31.6    | 0.020   |
|                                   | Mortality, %              | 55.6                 | 52.2                | 59.1    | 0.767   |

Data are presented as median (interquartile range) unless otherwise indicated. Missing values were as follows: age (0), sex (5), dialysis vintage (11), transplant vintage (11), diabetes mellitus (19), vitamin K antagonist (26), previous parathyroidectomy (24), immunosuppression (13), lesion location (12), clinical manifestations (12), creatinine (12), total calcium (10), phosphate (13), Ca × P (4), PTH (13), histological confirmation (7), treatment (9) and outcome (0). Values in bold are statistically significant.

ESRD history. The whole-population dialysis and transplant vintage were 24 (12–72) and 20 (4–48) months, respectively. Patients diagnosed after 2000 had a longer dialysis vintage in comparison with a tendency for those patients diagnosed before 2000 for a shorter period [18 (10–51) versus 30 (13–120) months; P = 0.059]. The transplant vintage before the appearance of calciphylaxis lesions was not different between groups [12.5 (4.75–39) versus 24 (1.87–63.75) months before and after 2000, respectively; P = 0.431]. It has to be noted that almost in half of the cases (43.2%), calciphylaxis developed during the first year after KT and 15.5% during the first month. Total renal replacement therapy time was longer in patients diagnosed after 2000 [73.2 (16–192) versus 20.25 (12.5–78) months; P = 0.045].

Risk factors for calciphylaxis. In most cases diagnosed before 2000, the comorbid conditions were not reported. Among the other group of patients, 23.8% had diabetes mellitus, 23.8% underwent a previous parathyroidectomy and 42.9% were receiving treatment with vitamin K inhibitors.

Immunosuppressive treatment. The immunosuppressive scheme changed considerably over time. Before 2000, it was based on azathioprine (AZA) in 66.7% of cases and on CNI only in 33.3% of cases. Afterwards, CNI were employed in 72.2% of patients, as well as MPA (50.0%) and mTORi (44.4%). Steroids were always used (100.0%), irrespective of time period.
Calciphylaxis after kidney transplantation

Clinical manifestation and lesion location. Purpura and ulcers were the most frequent form of clinical presentation in the whole population, each one accounting for 33.3% of cases. Purpura was most frequently observed in cases reported before 2000 (58.3%), while after 2000, the most frequent presentation was that of ulcers (38.1%), followed by purpura and necrosis (19.0%) each. In most cases (63.6%) lesions developed in distal areas, while proximal localization was most frequently reported before 2000 (58.3% versus 23.8%; \( P = 0.067 \)). Calciphylaxis was confirmed by skin biopsy in 68.4% of cases. Representative images of vascular calcification assessed by low-energy X-rays (mammographic technique) are displayed in Figure 3, while histological images of the same patients are displayed in Figure 4.

Laboratory findings. Median creatinine at diagnosis was 2.4 (1.25–4.64) mg/dL, without differences between groups [2.4 (1.3–6.6) versus 2.25 (1.13–3.45); \( P = 0.735 \)]. Patients diagnosed before 2000 had higher serum calcium [10.25 (9.42–10.72) versus 9.40 (8.80–9.90); \( P = 0.020 \)] and a tendency towards lower serum phosphate [3.55 (3.00–4.20) versus 4.33 (3.48–5.25); \( P = 0.077 \)]. Serum PTH levels were above 500 pg/mL in 50% of cases and below 100 pg/mL in 25.0% of cases, without significant differences between time periods.

Calciphylaxis treatment. Medical treatment for calciphylaxis was not reported in most of the first cases reported in the literature. After 2000, treatments reported included sodium thiosulphate (42.6%) and bisphosphonates (36.8%); calcimimetics (cinacalcet) were also used in 31.6% of cases. Regarding the surgical treatment, it was significantly different between the two time frames. Parathyroidectomy was performed in 61.9% of patients diagnosed in the first period, while it was performed only in 10.5% of cases in the second period (\( P = 0.001 \)). Mortality was similar between both groups (52.2% versus 59.1%, \( P = 0.767 \)).

DISCUSSION

Calciphylaxis is a condition that has been typically associated with ESRD patients, because a major factor in its development is the ureamic milieu characteristic of this population. In this regard, chronic uraemia seems to play a major role in the development of the disease, since it promotes the calcification process and it is associated with coagulation abnormalities [2]. However, some cases have been described in patients with normal renal function who have severe vasculopathy or chronic systemic inflammatory conditions [3, 4], which are known to play a major role in transdifferentiation of vascular smooth muscle cells (VSMCs) into cells of osteogenic lineage [32].

In this regard, calciphylaxis cannot be considered only the consequence of long-standing uraemia, and the term CUA may lead to disagreement and misclassification. It should be interpreted as the clinical syndrome caused by critical ischaemia of calcified terminal skin (candelabra) arteries, independently of whether the cause of chronic vascular calcification has been uraemia, chronic inflammation, ageing, pharmacological, genetic predisposition or all of them in combination. In this context, the development of calciphylaxis in kidney transplant recipients represents a unique context in which uraemia has been healed by the restored renal function but, in spite of that, the syndrome ensues.

Herein, we present the largest series of calciphylaxis in kidney transplant recipients reported so far to our knowledge (\( n = 14 \), Table 1). Combining it with the other cases reported so far, they sum up for a total of 45 cases. In the local series, no more data were available on patients already described in 1998 (\( n = 7 \)), but we could provide more granular data on patients diagnosed during the last two decades (\( n = 7 \)), in which demographic characteristics are coherent with the most recent series reported in the literature [33]. In the latter subcohort (Table 2), calciphylaxis was associated with moderate graft dysfunction; most patients had already been transplanted before, and they also had a long dialysis and transplantation vintage. It should be noted that four of seven patients were carrying vitamin K inhibitors, a known risk factor for the development of the syndrome [34]. Mineral metabolism was deranged as expected, with four patients having PTH of >900 pg/mL and one having undergone parathyroidectomy before transplant. In all cases, the location of the lesion was distal, presenting with either necrosis or ulcers. Treatment was multimodal in most cases and included different combinations of bisphosphonates, thiosulphate and cinacalcet. We observed 28.6% of mortality in our series, lower than that reported in the literature.

Examining our data along with all the other reported cases (\( n = 45 \)), a time-dependent pattern becomes evident as the large time frame of 50 years (1969–2019) roughly includes almost all the history of KT, thus patients’ characteristics and treatment varied widely according to the time-point.

From the historical point of view, tremendous strides have been made in transplant immunology and immunosuppression. The introduction of MPA mofetil and tacrolimus in the 1990s marked a ‘before’ and ‘after’ in the history of KT.
FIGURE 3: Radiological findings of calciphylaxis in three representative cases of kidney transplant recipients of Hospital Clinic’s population. (A) Patient number 1: X-ray with mammographic technique of lower leg showing vascular and scattered calcifications in the calf. (B) Patient number 4: X-ray with mammographic technique of leg showing extensive tibial and fibular arteries calcifications. (C) Patient number 6: X-ray with mammographic technique of lower leg and ankle showing extensive vascular calcifications.

tacrolimus gradually supplanted cyclosporine, and MPA mofetil replaced AZA almost universally [35]. For this reason and according to the distribution of the published series (Figure 1), we chose as a cut-off in our study the year 2000. We observed specifically that in the early era (before 2000) patients who developed calciphylaxis were younger with a shorter CKD vintage. As expected, immunosuppression was based on AZA and prednisone in most of the cases, while after 2000 the majority of patients were taking CNI associated with either mTORi or MPA. We observed higher calcium and lower phosphate in patients diagnosed before 2000, probably due to a tendency to higher PTH. In the early era, lesions were more likely to be proximal and more purpura was noted. Regarding treatment, it is interesting that the treatment of choice in 61.9% of patients diagnosed before 2000 was parathyroidectomy, while treatment with thiosulfate was introduced more recently [26]. This probably reflects the knowledge of the disease at that time; nowadays it is clear that calciphylaxis is multifactorial, but before it was thought to be caused only by hyperparathyroidism [6, 11]. This notion is contrasted by the fact that a total 25.0% of patients underwent parathyroidectomy before and that PTH at diagnosis was <100 pg/mL in a quarter of cases. Overall mortality reported was 55.6%, a finding coherent with the experience with calciphylaxis in end-stage renal disease [34].

Taken together, these data suggest that, in some patients, calcification of the small arteries of the skin does not halt or slow down after kidney transplant, even though available data focus on large vessels (coronaries and aorta) [5]. One major factor could be the presence of vascular calcifications before KT; it seems that patients without previous calcifications are less likely to develop de novo lesions, while in those patients who have already developed calcifications before transplant, these often progress afterwards [36, 37]. Factors associated with the progression of vascular calcification include classical Framingham risk factors, graft function, age, dialysis vintage, mineral metabolism, systemic inflammation and genetic propensity [1]. A specific characteristic of this population is immunosuppression, which may also be involved in vascular calcification [5, 22]. A defined role played by immunosuppressive drugs is related to altered glucose and lipid metabolism; in particular steroids, CNI and mTORi are associated with post-transplant diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia, all of which are risk factors for atherosclerosis and vascular calcification progression [38]. A more speculative mechanism is related to the action exerted by immunosuppressive drugs at the level of the endothelium. In this regard, CNI may exert a detrimental effect by inhibiting nitric-oxide-mediated vasodilation [5], while mTORi could stabilize the atherosclerotic plaque [39]. Another mechanism probably involved is the altered Receptor Activator for Nuclear Factor κ B (RANK)-dependent transdifferentiation of VSMCs into osteoblasts that is inhibited by osteoprotegerin (OPG), thus preventing the binding of Receptor Activator for Nuclear Factor κ B Ligand (RANKL) to its natural receptor RANK. Osteoclasts precursors exposed to the mTORi sirolimus express significantly higher levels of OPG mRNA, while tacrolimus reduced it [40].

It should be noted that more than half of patients developed calciphylaxis during the first year after KT and seven (15.5%) during the first month (patient number 4 and 6 of the local series and references [8, 9, 14, 24, 27]). It is likely that this subset of patients already had a severely calcified vasculature and intercurrent events soon after transplantation precipitated skin vessel
thrombosis or accelerated the calcification process. In the other cases, it is evident that the calcification process progressed after KT. We may speculate that in patients with an already calcified vasculature, the action of traditional (Framingham) and non-traditional risk factors (graft dysfunction, mineral metabolism, immunosuppression, etc.) could favour the progression of skin vessel calcification, eventually leading to the development of the clinical syndrome late after KT (Figure 5).

In conclusion, calciphylaxis is a syndrome that is not specific to patients on dialysis and might also occur in kidney transplant recipients with a functioning graft. Patients’ characteristics and treatment vary widely according to the time-point studied and reflect evolution of KT from the early era to date. Given the high mortality and the rarity of the disease, it would be desirable in the future to share patients’ data in international registries and to refine management by...
studying the pathogenesis more thoroughly and introducing new drugs.

**CONFLICT OF INTEREST STATEMENT**

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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**FIGURE 5:** Proposed pathophysiology for the development of calciphylaxis after kidney transplantation.
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