Cutaneous Calcification in Patients With End-Stage Renal Disease

A Regulated Process Associated With In Situ Osteopontin Expression

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EVERE CUTANEOUS CALCIFICATION develops mainly in patients with end-stage renal disease (ESRD). The pathogenesis is still unknown, which may explain the diverse terminology: calciphylaxis, calcific uremic arteriolopathy or azotemic arteriopathy, calcifying panniculitis, metastatic calcinosis cutis (CC), and others.

The annual incidence of CC in ESRD has been found to be approximately 1%. This condition generally consists of painful, purple skin lesions with purpura and livedo reticularis, progressing to nonhealing ulcers and soft tissue necrosis. The poor outcome of this syndrome, called calciphylaxis, is often associated with progressive microvascular and soft tissue deposition of crystalline apatite (calcium phosphate). Occasionally, the painful, indurated skin and subcutaneous lesions become circumscribed, and the condition is then called calcifying panniculitis. Finally, CC in patients with ESRD may acquire the form of metastatic CC with flexural infiltrating plaques.

Although the frequency of CC in ESRD has been reported to increase with the longevity of the patients, it is rare in comparison with noncutaneous vascular calcification, which occurs in 20% to 40% of patients and probably results from both medial and intimal calcification. Indeed, medial calcification of noncutaneous blood vessels is a striking feature of ESRD vascular disease, which is often associated with the common risk factors of age, diabetes mellitus, time since dialysis therapy began, dyslipidemia, arterial hypertension, hyperhomocysteinemia, hyperphosphatemia, high calcium-phosphorus product (Ca × P), hyperparathyroidism, and excessive daily intake of calcium salts. On the other hand, atherosclerotic vascular disease is a major cause of morbidity and mortality in patients with ESRD and could be also involved in vascular calcification. Significantly, in 2 case-control studies, independent risk factors for CC were female sex, low levels of serum albumin, high serum phosphate levels, high levels of total alkaline phosphatase, and morbid obesity. Hypoalbuminemia could be related to malnutrition and infection and/or inflammation, which in turn could accelerate atherosclerosis. Factors relating to media or atherosclerotic calcification might therefore be involved in the pathogenesis of CC.

Recent studies have shown that vascular calcification is an active and regulated process both in the context of ath-
erosclerotic plaque formation and in Monckeberg sclerosis with calcium deposition in the vascular media layer. It occurs mostly because of the transformation of smooth muscle vascular cells, or myofibroblasts, into osteoblastlike cells that express most of the noncollagenous bone matrix proteins, such as alkaline phosphatase, osteopontin, osteonectin, bone sialoprotein, and bone morphomeric proteins.5,10 This phenomenon might occur via the activation of Msx2-signaling that promotes both the osteogenic differentiation of vascular cells and the modulation of circulating osteopontin levels.6

For instance, osteopontin is a secreted phosphoprotein adhesion molecule with high affinity for calcium ions. It has already been associated with the pathologic mineralization of soft tissues, such as heart valves11,12 and the tunica media of vessels in dialysis patients.13 Ahmed et al13 provided no information on osteopontin deposits in the dermis or subcutaneous tissues or of staining in the intima of vessels with lesions. It has also been shown that uremic serum and phosphorus up-regulate osteopontin expression in vascular smooth muscle cells.14 Osteopontin deposition has also been implicated in the calcification process of the benign cutaneous tumor called pilomatrixoma.13 It has also been associated with the mineralization of dermal elastic fibers in patients with pseudoxanthoma elasticum.15

To gain further insight into the mechanisms leading to CC in ESRD, we conducted a retrospective study of all CC seen in the last 10 years in our center. We analyzed their clinical, biological, and histopathologic features as well as the in situ expression of osteopontin in cutaneous biopsy specimens from 9 patients.

## METHODS

This is a retrospective study of all patients with ESRD and CC admitted to the dermatology department of Saint-Louis Hospital (Paris, France) from 1990 to 2000 and for whom archival biopsy specimens were available. The demographic data of the 9 patients, including age, sex, type of nephropathy, underlying disease, duration of dialysis, transplantation, and the evolution of CC are summarized in **Table 1**. The types of cutaneous lesions from each patient are listed in **Table 2**. Plasma calcium levels were determined using atomic absorption spectrometry and measuring plasma phosphorus levels with a Technicon Auto Analyzer (Vineland, NJ). Serum intact parathyroid hormone (iPTH) concentrations were measured by a commercial radioimmunometric assay for human iPTH 1 to 84 (Allegro Intact PTH; Nichols Institute, San Juan Capistrano, Calif.). The range of normal values was 10 to 70 pg/mL. Total plasma alkaline phosphatases (tAP) were measured by an automated method (normal range, 73 to 207 IU/L). Plasma vitamin D and 1,25 hydroxyvitamin D were measured by radioimmunometric assay as previously described.17,18 Normal ranges for plasma vitamin D levels are 10 to 40 ng/mL, and for 1,25 hydroxyvitamin D, 20 to 60 pg/mL. Serum osteocalcin was measured by an immunoradiometric assay (ELSA-OSTEO; Cis Bio- international, Gif-sur-Yvette, France). Normal values for plasma vitamin D ranged from 10 to 55 ng/mL.

Archival formalin–paraffin-embedded biopsy specimens from all patients were reviewed. Patients were informed of this research protocol according to the institution’s regulations. Biopsy sections were stained with hematoxylin-eosin for mor-

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**Table 1. Demographic and Clinical Data From 9 Cases of ESRD With Cutaneous Calcification**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Type of Nephropathy</th>
<th>Underlying Disease</th>
<th>Duration of Dialysis, y</th>
<th>Kidney Transplantation</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/64</td>
<td>Vascular</td>
<td>Diabetes</td>
<td>7</td>
<td>No</td>
<td>Remission after dialysis with lower calcium (Ca²⁺) levels (1.5 mmol/L)</td>
</tr>
<tr>
<td>2/F/51</td>
<td>AA amyloidosis</td>
<td>Phlebitis</td>
<td>7</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>3/F/76</td>
<td>Vascular</td>
<td>Polyarthritis</td>
<td>4</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>4/F/59</td>
<td>Unknown</td>
<td>Lower extremity arthritis, diabetes</td>
<td>4</td>
<td>No</td>
<td>Remission parathyroidectomy</td>
</tr>
<tr>
<td>5/F/66</td>
<td>Diabetes</td>
<td>Obesity</td>
<td>1</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>6/F/62</td>
<td>Autosomal dominant polycystosis</td>
<td>Obesity</td>
<td>4</td>
<td>No</td>
<td>Remission parathyroidectomy</td>
</tr>
<tr>
<td>7/M/39</td>
<td>IgA glomerulonephritis</td>
<td>Hepatitis C</td>
<td>6</td>
<td>Yes (11 y before calcinosis), chronic rejection</td>
<td>Remission parathyroidectomy</td>
</tr>
<tr>
<td>8/F/65</td>
<td>AL amyloidosis</td>
<td>Nephrotic syndrome</td>
<td>1</td>
<td>No</td>
<td>Remission after LMWH replaced</td>
</tr>
<tr>
<td>9/F/68</td>
<td>Urologic malformation</td>
<td>Hypothalamic teratoma</td>
<td>3</td>
<td>Yes (4 mo before calcinosis), chronic rejection</td>
<td>Spontaneous remission</td>
</tr>
</tbody>
</table>

Abbreviations: AA, amyloid A protein; AL, amyloid light-chain protein; ESRD, end-stage renal disease; LMWH, low-molecular-weight heparin; MGUS, monoclonal gammopathy of unknown significance.
phologic study and with von Kossa stain for detection of calcification. The sections were analyzed blindly by 2 pathologists for the presence of endovascular fibrosis, the type of vessel with calcification, and the topography of calcium deposit within the vessel wall. We also studied the extravascular tissue.

Immunostaining for osteopontin was performed using immunoperoxidase and the avidin-biotin complex technique with 3,3′-diamino-benzidine as chromogen on 3-µm paraffin-embedded sections. The anti-osteopontin antibody (Eurod君子, Mundolsheim, France), at 1:50 dilution, was used. Antigen retrieval was by 3×5-minute microwave treatment in citrate buffer at pH 6.

RESULTS

Between 1990 and 2000, 9 patients with CC were examined in the dermatology department of our institution. The median age was 64 years (range, 39-76 years). There were 8 women and 1 man. All patients but 1 were white. The underlying renal diseases were as follows: vascular or hypertensive nephropathy, 2; unknown, 1; amyloidoses, 2; focal glomerulonephritis, 1; autosomal dominant polycystic kidney disease, 1; malformative uropathy, 1; and diabetes mellitus, 1. It is noteworthy that 3 of the 9 patients had diabetes mellitus and 2, amyloidosis. Comorbidity was also important: obesity (2 cases), monoclonal gammopathy of undetermined significance or myeloma (3 cases), thromboembolic disease related to activated protein C resistance to circulating anticoagulant (3 cases) (Table 1).

The clinical manifestations of CC can be summarized as follows: 7 patients had cutaneous painful ulceration of the leg (Figure 1), and 2 had panniculitis (Table 2).

The median plasma Ca×P was 4.95 mmol²/L² (range, 1.81-6.95 mmol²/L²) (Table 3). Significantly, in 5 of 9 patients, it was lower than 5.40 mmol²/L², a value regarded as a median threshold for coronary artery calcification in a series of patients with ESRD. Only 3 of 8 patients had significantly high serum iPTH levels (≥400 pg/mL) with increased plasma tAP levels suggestive of severe secondary hyperparathyroidism. Serum osteocalcin levels were increased in 3 of 5 patients for whom data were available. Plasma vitamin D and 1,25 hydroxyvitamin D₃ levels were low in 4 of 6 and 3 of 6 patients, respectively, while aluminum levels were normal in all of the patients.

Three patients died from either sepsis or complications of decubitus. In 6 patients, the clinical signs of CC partially or totally regressed after parathyroidectomy (n=3) or after modifying the vitamin D therapy and decreasing the calcium concentration of the dialysis fluid. Pathologic features are summarized in Table 2. We observed sepsal inflammation in 8 of 9 patients. Calcification of subcutaneous vessels was found in all patients. Calcium deposits were localized in the media and some-

### Table 2. Histopathologic Data From 9 Cases of ESRD With Cutaneous Calcification

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Septal Subcutaneous Inflammation</th>
<th>Calciﬁed Dermal Vessels</th>
<th>Calciﬁed Subcutaneous Vessels</th>
<th>Type of Calciﬁed Vessels</th>
<th>Fat Necrosis</th>
<th>Extravascular Calcification</th>
<th>Endovascular Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Necrotic ulcers of the legs</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>Necrotic ulcers of the groin and limbs</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>A</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>Ulcers and livedo reticularis of the legs</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A, C</td>
<td>Present</td>
<td>N, S</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>Necrotic ulcer of the legs</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A</td>
<td>Absent</td>
<td>M</td>
<td>Present</td>
</tr>
<tr>
<td>5</td>
<td>Abdominal and genital ulcers</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A, C</td>
<td>Present</td>
<td>M</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>Painful nodules on the legs</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>7</td>
<td>Painful nodules on the legs</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>8</td>
<td>Necrotic ulcers at the injection sites of LMWH</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>A, C</td>
<td>Present</td>
<td>M</td>
<td>Present</td>
</tr>
<tr>
<td>9</td>
<td>Necrotic ulcers of the abdomen</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>A, C</td>
<td>Present</td>
<td>S</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Abbreviations: A, arteriole; C, capillaries; ESRD, end-stage renal disease; LMWH, low-molecular-weight heparin; M, macrophages; N, nerves; S, sweat gland.

Figure 1. Deep ulceration of the thigh in patient 2, exposing necrotic panniculus adiposus.

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times in the intima (Figure 2A). In 2 cases, capillaries were also calcified (Figure 2D). Endovascular fibrosis was observed in 5 cases (Figure 2B). In those with extensive vascular calcification and fat necrosis, there were extravascular calcium deposits in the subcutaneous interlobular septae, between adipocytes (Figure 2C), and sometimes around nerves or sweat glands.

Osteopontin staining occurred in 8 of 8 patients with CC. It was localized either in the intimal (Figure 2B) or medial tunica (Figure 3A) or in both. Osteopontin staining was also observed in subcutaneous tissue. Occasionally, it was also found in sweat glands (Figure 3G), nerves (Figure 3F), and macrophages (Figure 3E). In fact, osteopontin staining was associated with calcium deposits except in macrophages. No osteopontin staining was observed in skin biopsy specimens from the 3 patients with ESRD without calcinosis (1 pruritus, 1 infectious cellulitis, and 1 benign tumor).

**COMMENT**

Calcinosis cutis in ESRD is a severe condition with mortality rates as high as 80%.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Albumin, g/L (39-48)</th>
<th>Calcium, mmol/L (2.20-2.60)</th>
<th>Phosphorus, mmol/L (0.9-1.5)</th>
<th>Ca × P, mmol²/L</th>
<th>iPTH, pg/mL (10-60)</th>
<th>tAP, IU/L (90-280)</th>
<th>Osteocalcin, ng/mL (10-30)</th>
<th>Vitamin D, ng/mL (10-40)</th>
<th>1,25-Dihydroxyvitamin D₃, pg/mL (20-60)</th>
<th>Aluminum, µmol/L (&lt;0.40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>2.20</td>
<td>2.25</td>
<td>4.95</td>
<td>413</td>
<td>150</td>
<td>ND</td>
<td>11</td>
<td>4</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>2.51</td>
<td>2.29</td>
<td>5.75</td>
<td>181</td>
<td>124</td>
<td>13</td>
<td>ND</td>
<td>19</td>
<td>0.30</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>2.29</td>
<td>2.80</td>
<td>6.41</td>
<td>115</td>
<td>30</td>
<td>20.4</td>
<td>5</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>2.67</td>
<td>1.21</td>
<td>3.23</td>
<td>1223</td>
<td>938</td>
<td>807</td>
<td>11</td>
<td>24</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>2.52</td>
<td>1.25</td>
<td>3.15</td>
<td>18</td>
<td>188</td>
<td>ND</td>
<td>3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>2.14</td>
<td>2.89</td>
<td>6.18</td>
<td>517</td>
<td>305</td>
<td>278</td>
<td>3.7</td>
<td>22</td>
<td>0.11</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>2.80</td>
<td>2.48</td>
<td>6.94</td>
<td>267</td>
<td>109</td>
<td>57.8</td>
<td>5</td>
<td>11</td>
<td>0.37</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>1.81</td>
<td>1.00</td>
<td>1.81</td>
<td>8.5</td>
<td>150</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>2.29</td>
<td>2.03</td>
<td>4.65</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Median for all patients</td>
<td>33</td>
<td>2.29</td>
<td>2.25</td>
<td>4.95</td>
<td>181</td>
<td>150</td>
<td>57</td>
<td>11</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Circulating Biochemical Data From 9 Cases of ESRD With Cutaneous Calcification**

*All data are reported in indicated units; normal ranges appear in parentheses in column heads for reference.*

Calcinosis cutis occurred after a short period of dialysis (median period, 4 years; range, 1-7 years) or in transplantation patients with poor graft function (2 cases). This may be considered against a median delay in renal re-
placement of 3.2 years and 4.2 years noted in 2 recent studies.8,9

Vascular comorbidities were frequent in our patients, not only diabetes mellitus, whether or not associated with obesity as shown in other studies,8,9 but 2 patients had amyloidosis or coagulation disorders. Female sex, which predominates in our series, has also been independently associated with a higher risk of CC.8

Signs of secondary hyperparathyroidism were present in only 3 patients and were associated with good clinical outcome after parathyroidectomy. Calcinosi cutis and cardiovascular calcifications have been associated with a Ca × P greater than 5.50 mmol²/L² and with increased serum phosphate concentrations.8 However, serum Ca × P was above the saturation threshold in only 4 of our 9 patients, of whom 2 had subnormal iPTH values. Moreover, serum phosphate levels were normal for 3 patients whose Ca × Ps were below the saturation threshold. Therefore, CC can be observed in patients with ESRD with a normal or even a low Ca × P and a normal serum phosphate value.

In this series, 6 of 9 patients were cured after either lowering the calcium concentration of the dialysis fluid or surgical correction of the secondary hyperparathyroidism, which represents a better result than is reported in the literature.8,9,13 Non–calcium-free phosphate binding agents, such as sevelamer, as proposed by Chertow et al,21 were used in our patients. The long-term effects of sevelamer hydrochloride on the Ca × P and the prevention of CC in hemodialysis patients remain to be determined.

Skin biopsy and histologic examination of CC lesions are the only way to reliably diagnose CC. Our study stresses the importance of vascular lesions and provides a precise description of the types of vessels and the different techniques used. It also shows the importance of extravascular lesions in very severe cases. In accordance with previous reports, intravascular calcium deposition within the media of subcutaneous and dermal vessels was a constant feature in our patients.20,22,23 This suggests that media calcification is probably the first event in the process of CC. An endovascular fibrosis was often, but not always, associated with this media calcium deposition and probably followed the inflammatory reaction to the media calcification. In some patients, intense calcium deposits led to complete vessel occlusion.

Furthermore, additional capillary calcification was observed in some cases. Such calcification of capillaries devoid of media probably followed the extension of calcification from contiguous arteriolar vessels. On the other hand, the mechanisms involved in atherosclerosis, which typically affect the intima, could also be involved. Moreover, in the cases of severe CC with a fatal outcome, we noticed extensive extravascular calcium deposits in li-
ocytes, nerves, and sweat glands. Such extravascular calcium deposits have been rarely described in CC. This suggests that other factors are involved in CC, including fat necrosis following ischemia due to occluded calcified vessels, as seen in a variety of inflammatory diseases (for instance, connective tissue disorders). Ischemia probably explains the predominance of lesions in subcutaneous tissue, which is less well supplied with blood vessels than other tissues, particularly in obese patients who are clearly at higher risk for CC.

The immunohistochemical studies performed on 8 of 9 patients revealed expression of osteopontin, a noncollagenous protein that inhibits extracellular matrix mineralization. To our knowledge, only 2 studies have been published on osteopontin expression and CC in ESRD, and our results allow us to clarify the different cell types expressing osteopontin in this condition. Osteopontin was shown in all calcified vessels. Furthermore, it was also shown in the walls of 1 uncalcified vessel, suggesting that it might represent an early marker for calciﬁphaxis, which should be further evaluated. It was noteworthy that, as with calcium deposits, osteopontin predominates in the media of the vessels, although it can sometimes be also found in the intima. Similarly, osteopontin was associated with intima not only in calciﬁphaxis specimens but also in atherosclerotic vessels from patients with ESRD, as was demonstrated by Canﬁeld et al. These results contrast with previous ﬁndings that osteopontin staining was only to be detected in the media layer.

Osteopontin was detected around all extravascular calcium deposits. Indeed, it was detected within calcified sweat glands and nerves in 1 patient. To the best of our knowledge, its involvement in sweat glands from normal or pathologic skin has never been reported. It might be related to osteopontin and calcium deposits within vasa vasorum or vasa nervorum perfusing sweat glands or nerves.

Thus, osteopontin staining was observed within all vascular and extravascular calciﬁcation lesions. Moreover, we also detected osteopontin within macrophage cytoplasm from the subcutaneous tissue of 2 patients. To our knowledge, this is the ﬁrst time that osteopontin expression by macrophages has been reported in patients with calciﬁphaxis. Recently, macrophages surrounding the ath- eromatous plaques of aortic calciﬁcation in hemodialysis patients were identiﬁed as expressing osteopontin. These ﬁndings may be compared with those of Hirota et al on pilomatrixomas. These are common, benign epidermal appendage tumors composed of hair-matrix basaloid cells, which are progressively transformed to shadow cells with a simultaneous foreign body reaction and calciﬁcation in the stroma. Hirota et al found a colocalization of calcium phosphate deposits and osteopontin expression in CD68-positive macrophages surrounding the shadow cell nests.

The predominance of calcium deposits within the media and the presence of osteopontin within CC strongly suggest that these phenomena are actively regulated processes beginning in the media. Passive calcium deposits due to an abnormal serum Ca × P would begin in the intima. Moreover, 5 of 9 patients had a Ca × P below the saturating threshold, and this fact points to an active, not passive, calciﬁcation. The presence of other proteins involved in calciﬁcation, such as matrix gamma-carboxylglutamic acid protein, thrombospordin-1, and cartilage oligomeric matrix protein in CC in patients with ESRD, strengthens the hypothesis of a regulated process.

Osteopontin dysregulation could occur in CC and lead to a defective inhibition of calciﬁcation. A prospective evaluation of early and late CC should be done to obtain a dynamic overview of osteopontin expression and to determine whether osteopontin staining is an early marker of calcium deposition. However, according Canﬁeld et al, understanding the role of osteopontin in CC requires understanding its phosphorylation status, since phosphorylated osteopontin inhibits calciﬁcation, whereas unphosphorylated osteopontin enhances it.

In conclusion, our ﬁndings of CC in patients without major serum calcium or phosphate measurement abnormalities and of calcium deposits and osteopontin in the media favor an active role of vascular muscle cells as in Monckeberg sclerosis. Clinical data combined with in vitro transformation of vascular muscle cells into osteoblasts in the presence of elevated concentrations of inorganic phosphorus strongly suggest that CC is associated with an osteogenic differentiation of vascular muscle cells. Further studies are needed to deﬁne the preventing role of non–calcium-free phosphate binding agents and the therapeutic value in CC of osteoclastic resorption inhibitors such as biphosphonate and osteoprotegerin known to block media arterial calciﬁcations in rat models.

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