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Expert Review

Management of Calcinosis Cutis in Rheumatic Diseases

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ABSTRACT. Calcinosis (hydroxyapatite and calcium phosphate crystal deposition) within the extracellular matrix of the dermis and subcutaneous tissue is a frequent manifestation of adult and pediatric systemic autoimmune rheumatic diseases, specifically systemic sclerosis, dermatomyositis, mixed connective tissue disease, and systemic lupus erythematosus. In this article, we review classification of calcinosis, highlight mechanisms that may contribute to the pathogenesis of calcinosis, and summarize the evidence evaluating nonpharmacologic and pharmacologic interventions for the treatment of calcinosis.

Key Indexing Terms: calcinosis cutis, scleroderma, systemic sclerosis

Calcinosis cutis refers to deposition of calcium salts in the skin. The condition is divided into 5 types, with dystrophic calcinosis cutis being the most common form. It appears as a result of local tissue damage or abnormalities, such as alterations in collagen, elastin, or subcutaneous fat. Dystrophic calcification usually occurs in association with several adult and pediatric systemic autoimmune rheumatic diseases (SARDs). The most frequent rheumatic diseases (RDs) are systemic sclerosis (SSc) and dermatomyositis (DM),[1] followed by mixed connective tissue disease, and rarely, systemic lupus erythematosus.[2]

Calcinosis in SSc is characterized by hydroxyapatite and amorphous calcium phosphate crystal deposition[3] in the extracellular matrix of the dermis, subcutaneous tissue, and other tissues, whereas in DM, the mineral present in calcinosis deposits consist of carbonate apatite.[4] There is no cure for calcinosis, and it remains a therapeutic challenge in patients with RDs. In this article, we outline our approach to the evaluation, diagnosis, and management of calcinosis. We summarize the evidence supporting pharmacologic interventions and nonpharmacologic treatments for calcinosis.

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Current understanding of calcinosis in rheumatic diseases

Classification. Boulmann et al[5] classified the soft tissue classification into 5 subtypes: dystrophic, metastatic, idiopathic, tumoral, and calciphylaxis (Table 1). SARDs are mainly associated with dystrophic calcification,[2] which is characterized by deposition of calcified material in damaged tissue, with normal serum calcium and phosphate levels[2] (Figure 1 and Figure 2). The term *calcinosis circumscripta* is used to describe calcinosis limited to an extremity or joint. Calcinosis universalis occurs when there is diffuse involvement of muscles and tendons.[6]

Epidemiology. The prevalence of calcinosis ranges from 18% to 49% in patients with SSc,[7-9] with a similar prevalence in limited cutaneous SSc (lcSSc) and diffuse cutaneous (dcSSc).[10] Although initially believed to be more common in lcSSc, more recent evidence shows that calcinosis occurs to a similar degree in all SSc cutaneous subtypes, with no preponderance in lcSSc. For example, a large cohort found an increased risk of calcinosis in patients with dcSSc and those with antipolymerase III antibody positivity.[11] Calcinosis cutis results from the deposition of insoluble calcium hydroxyapatite and amorphous calcium phosphate crystals within the extracellular matrix of the dermis and subcutaneous tissue.[12] Risk factors for calcinosis in SSc include long disease duration.[10,13,14] Its progression is more common in men[15] and in patients with digital ulcers (DUs), osteoporosis, and internal organ involvement, specifically interstitial lung disease (ILD).[16,17] Calcinosis is a long-term, debilitating manifestation of these diseases that adversely affects quality of life.[18-21] While anticentromere antibody positivity[22] has long been associated with calcinosis in SSc, the presence of anti-PM/Scl antibodies has also been associated with a higher prevalence of calcinosis.[23]

Calcinosis cutis is seen in 30% of adult dermatomyositis (DM) cases and in up to 20% to 40% of juvenile DM (JDM) cases.[6] Calcinosis cutis typically arises within 2 to 3 years from the onset of JDM; this is faster than occurrence in other connective tissue disorders or in adult DM, which has an average onset of calcinosis cutis at approximately 8 years.[24] In JDM, the most common

Table 1. Classification of calcinosis cutis and associations.

Type of Calcification	Pathogenesis	Serum Calcium and/or Phosphorus Levels	Associated Diseases	Clinical Presentation
Dystrophic calcification	Secondary to tissue damage	Normal	Systemic sclerosis Dermatomyositis Lupus erythematosus Lupus panniculitis	Present as nodules, plaques, extensive small dermal, or large subcutaneous deposits
Metastatic calcification	Calcium precipitation in the skin	Abnormal	Chronic kidney failure Hyperparathyroidism Hypervitaminosis D sarcoidosis	Seen occasionally in the subcutaneous tissue as hard nodules located mainly in the vicinity of large joints
Idiopathic calcification	Unknown; no previous damage to skin or metabolic disturbances	Normal	Tumoral calcinosis Calcified subepidermal nodules (Winer's nodular calcinosis) Scrotal calcinosis	Multiple, asymptomatic nodules, which begin to appear in childhood or in early adult life
Tumoral calcification		In patients with an elevated serum phosphorus level but normal calcium level		Presents as large subcutaneous calcium deposits near joints and pressure areas
Calciphylaxis	Calcification of the small vessel walls in the dermis and subcutaneous tissue, with subsequent ischemia	Abnormalities can be observed	Chronic kidney failure Other nonuremic causes	Subcutaneous nodules of infarction and necrotizing skin ulcers

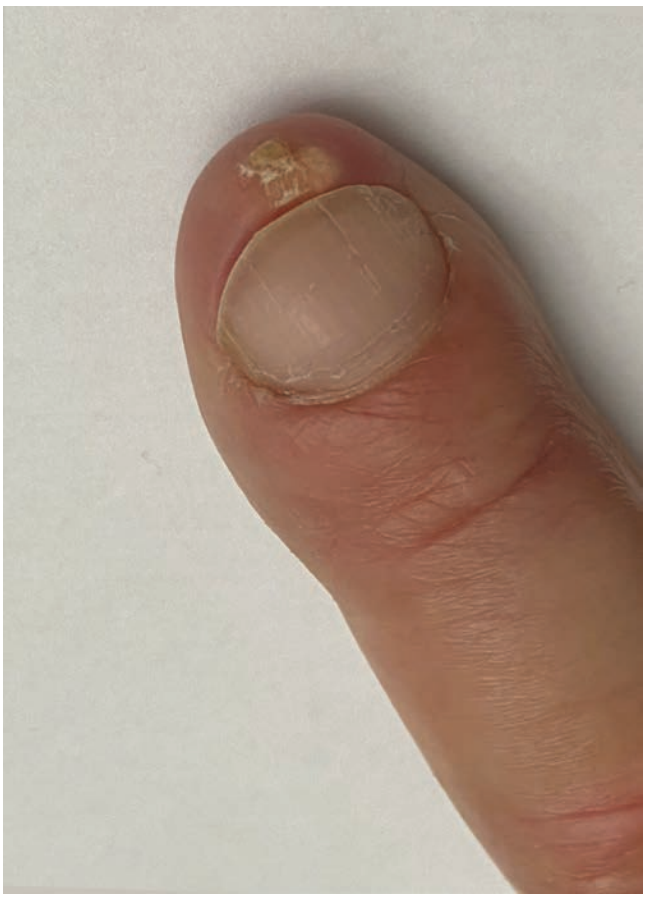

Figure 1. Calcinosis cutis in the soft tissue at the tip of the finger.

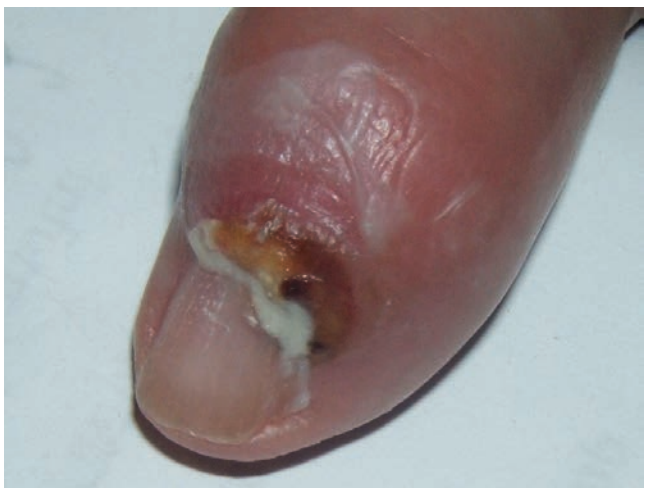

Figure 2. Liquified calcinosis draining from the soft tissue proximal to the fingernail.

antibodies are antitranscriptional intermediary factor 1-γ (anti-TIF1-γ) in 18% of the children, followed by antinuclear matrix protein 2 (anti-NXP2; 15%) and antimelanoma differentiation associated protein 5 (anti-MDA5; 6%).[25] Anti-NXP2 antibody has been associated with more severe muscle disease, younger age at onset, and increased risk of calcinosis.[25] Anti-PM/Scl antibodies are associated with an increased risk of calcinosis in both adult DM and JDM, whereas anti-TIF1-γ is associated with a decreased risk of calcinosis in adult DM.[26]

Pathophysiology. The pathophysiology behind dystrophic

calcification is unclear. Several mechanisms have been proposed, including chronic inflammation, vascular hypoxia, recurrent trauma, and abnormalities in bone matrix proteins. Elevated levels of serum interlukin (IL)-1, IL-6, IL-1b, and tumor necrosis factor support the role of inflammation in calcinosis development. Evidence demonstrated by Davis et al suggested an increased expression of hypoxia-associated glucose transporter 1 molecule in skin biopsies of patients with SSc with calcinosis,[27] contributing to the vascular ischemic theory (Table 2). Studies also reported elevated vascular endothelial growth factor (VEGF) levels, a potent angiogenic factor induced by hypoxia that is associated with increased osteoclast activity in SSc patients with calcinosis[28]; this finding suggests hypoxia-induced imbalance between angiogenic factors (such as VEGF and platelet-derived growth factors) and antiangiogenic factors (such as angiostatin and endostatin). This may be a factor in the pathogenesis of tissue fibrosis and calcinosis. This hypoxia-induced osteoclast activity in SSc may also be involved in the development of calcinosis (Table 2), possibly explaining the association between calcinosis and osteoporosis.[10,13,29]

Additionally, a frequent history of DUs[11,30] can be related to the vascular hypoxia and recurrent trauma hypotheses, with or without acro-osteolysis (Table 2).[16,17]

In addition, an increased expression of bone matrix proteins, such as osteonectin and matrix gamma-carboxyglutamic acid protein (MGP), were illustrated by Davies et al[31] in calcinotic skin of patients with SSc. These proteins are involved in ectopic calcification via upregulation of osteonectin, an activator of calcification, in the setting of suppressed levels of the inhibitor protein MGP. MGP must also be in its gamma-carboxylated form and bind to bone morphogenic protein 2 to inhibit calcification. This carboxylated form is vitamin K–dependent. Using studies of arterial calcifications, Wallin et al have proposed mechanisms in which oxidative stress, which is critical to microvascular injury in SSc, may inhibit vitamin K, resulting in undergamma-carboxylated and inactive MGP and causing dysregulated calcification (Table 2).[32]

Table 2. Summary of theories for the pathophysiology of calcinosis cutis.

Mechanism	Evidence
Chronic inflammation	Increased production of TNF, IL-1, IL-6, and other proinflammatory cytokines
Vascular hypoxia (ischemia)	Hypoxia-induced imbalance between angiogenic factors (such as VEGF, platelet-derived growth factors) and antiangiogenic factors (such as angiostatin, endostatin) Increased expression of the hypoxia-associated GLUT-1 Hypoxia-induced osteoclast activity
Recurrent trauma	Presence or history of digital ulcers Calcification occurs at sites of chronic trauma/stress, suggesting a role of pressure or recurrent trauma

GLUT-1: glucose transporter 1; IL: interleukin; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor.

Evaluation and diagnosis of calcinosis. Clinically, calcinosis in SSc presents as subcutaneous nodules in digits or at pressure points such as elbows, knees, or ischial tuberosities. Affected tissues can be the skin, subcutaneous fat, muscle, or tendons. Lesions usually range in size from a few millimeters up to centimeters. Calcinosis is frequently present in the hands (65-83%), preferentially affecting the dominant hand,[33] proximal upper extremity (27%), or in proximal lower extremity (10-22%), especially the hips (6.7%; Figure 1).[7,14] It can affect trunk, chest, buttocks, maxillary sinuses, spine, and paraspinal tissues.[7] Lesions may be asymptomatic, or associated with pain, soft tissue swelling, ulcers with superimposed infections, or even deformities leading to functional disability.[5] Calcinotic lesions can lead to compression neuropathies resulting in motor and/or sensory deficits.[34] Ulceration of the overlying skin may occur, with a higher tendency in the forearm, elbows, fingers (particularly the volar aspect of fingertips), metacarpophalangeal joints, or interphalangeal joints.

In DM associated with calcinosis, the affected areas include the extremities and trunk. Calcinosis can also develop in areas that were previously involved by the DM process, which may include muscle calcification. Dystrophic calcification in DM appears as small, localized nodules or papules, subcutaneous tumoral deposits, or intramuscular and fascial calcification sometimes leading to an exoskeleton formation that can limit joint movements.[5]

Calcinosis can be observed and felt on physical examination; however, imaging can confirm the diagnosis. Plain radiography is the first-line imaging modality. Ultrasound (US) is 89% sensitive in the detection of calcinosis.[35] Further experimental modalities include multidetector (MD-) computed tomography (CT), dual-energy CT, and magnetic resonance imaging. Favorably, MDCT provides better assessment, with a higher resolution and 3D images.[36] Previously, a radiographic scoring system[37] was developed to standardize the measurement of calcium deposits for hand calcinosis. Another method categorizes lesions according to the radiographic shape, pattern of lesions, and clinical appearances as 4 subtypes: mousse, stone, net, and plate.[14]

General approaches for the management of calcinosis

There is no cure for calcinosis, and it remains a therapeutic challenge in patients with RDs. We do not treat asymptomatic calcinosis pharmacologically. General measures include avoiding trauma and improving blood flow to the extremities, such as avoiding smoking and exposure to the cold and stress. Treatment of Raynaud phenomenon and DUs may have a preventive role in calcinosis.

If symptomatic with pain or skin breakdown, warm saltwater soaks may assist with extrusion of the calcinosis and prevent soft tissue infection. Pain and erythema can be signs of concomitant soft tissue infection. Topical antibiotics with lidocaine may treat minor soft tissue infection and relieve pain. Oral broad-spectrum antibiotics are required for moderate soft tissue infection, whereas intravenous (IV) antibiotics are required for progressive soft tissue infection or involvement of a tendon

sheath. Nonsteroidal antiinflammatory agents and opioids[38] may be used to relieve pain. The use of a temporary digital splint may protect the affected digit as many patients report pain when they inadvertently strike the affected area against a surface. In selected patients, we recommend a multidisciplinary approach where rheumatologists share care with dermatology, plastic surgery, infectious diseases, or occupational therapy, as needed. Solid calcinosis can liquify and ooze from the skin (Figure 2). Liquified calcinosis and resultant erythema and skin breakdown may appear as soft tissue infection. We recommend swabbing the drainage and sending the specimen for bacterial culture and antibiotic sensitivity assessment.

In the setting of JDM, calcinosis is considered a scarring lesion—the result of ongoing and accumulated damage due to inflammation (likely hypoxic). Thus, the best approach is to completely control inflammation, allow healing, and allow the body to reabsorb the calcium. Calcinotic lesion resorption over the years usually happens.[39] In contrast, the natural history of SSc-associated calcinosis is that few lesions improve while the majority either remain stable or progress at 1 year.[40]

Pharmacologic therapies for calcinosis

Several medical therapies have been studied for the treatment of calcinosis, using an array of study designs ranging from case reports and case series, to cohort studies and randomized trials. We use a cost-effective approach, using the least costly medications with the larger evidence base first (diltiazem, colchicine, minocycline). It is worth trying several of these options sequentially or as needed, as there is considerable variability among those who will or will not derive a therapeutic benefit and the magnitude of the response. The evidence to support these treatment options is summarized in Table 3, while the possible mechanisms of action are summarized in Table 4.

Diltiazem. Diltiazem, a commonly used calcium channel blocker, reduces intracellular calcium influx in affected tissues by influencing intracellular calcium levels in macrophage, thus potentially correcting the abnormal imbalance of intracellular calcium concentration that may lead to crystal formation. Early case reports showed encouraging positive results,[41-43] which were confirmed in a retrospective cohort study of 78 patients from the Mayo Clinic, the largest cohort of patients with calcinosis in autoimmune connective tissue diseases (ACTDs) studied to date.[44] Diltiazem was effective in 9 of 17 patients as first-line therapy for calcinosis.[44] However, a separate retrospective study[8] of 12 patients with SSc-related calcinosis treated with diltiazem showed no clinical benefit; only 3 patients showed a minor radiological improvement. No adverse effects (AEs) were found.[8] Similarly, no complete response was reported in a retrospective cohort study by Fredi et al (Table 3).[45]

Colchicine. Colchicine has an antiinflammatory effect by disturbing leukocyte chemotaxis and phagocytosis through inhibiting microtubule polymerization. In a patient with DM and a patient with SSc-associated calcinosis cutis, oral colchicine at a dose of 1 mg/day decreased inflammation and led to ulcer healing.[46] Colchicine also led to radiographic improvement of the calcified lesions in one of the patients. A retrospective review of 8 calcinosis patients treated with colchicine found that 3 responded positively, with 1 patient having a complete response.[44] Overall, colchicine may decrease symptoms of inflammation related to calcinosis, but with most patients having no change in calcification.

Warfarin. Warfarin, a vitamin K antagonist, has been proposed for treatment of calcinosis, based on the rationale that it reduces the levels of MGP (a vitamin K–dependent factor in the soft tissues) by preventing carboxylation of glutamic acid.[47] However, there is some concern that warfarin can promote calcification through undercarboxylated MGP.[47,48] Warfarin was evaluated in 1 randomized controlled trial (RCT)[49] and retrospective cohort studies.[44,45,50,51] In a study by Cukierman et al,[51] 3 patients with SSc-associated calcinosis were treated with low-dose warfarin for 1 year. Two of the patients improved with a complete resolution of calcinosis, while the third patient, who had larger and longer-standing calcinotic lesions, did not respond.[51] Balin et al[44] demonstrated that 4 of 19 ACTD patients with calcinosis who received warfarin had no improvement in calcinosis compared with the group that did not receive warfarin.

Berger et al[49] reported a small double-blind, placebo-controlled trial evaluating the effect of warfarin treatment for 18 months on extent of calcinosis based on clinical and radiographic examination. They found no evidence of a beneficial effect of warfarin.[49] However, they noted that warfarin decreased extraskeletal uptake on technetium 99m-diphosphonate whole-body nuclear scanning and decreased gamma-carboxyglutamic acid urinary concentration. Similarly, Lassoued et al[50] reported a small cohort study evaluating the effect of warfarin treatment on the extent of calcinosis based on clinical and radiographic (plain radiographs or CT) examination. They too found no clinical improvement in 6 patients (1 with SSc) with extensive and long-standing calcinosis treated with low-dose warfarin.[50] Five patients had clinical and radiological worsening of calcinosis.

Rituximab. The use of rituximab (RTX), a monoclonal anti-CD20 antibody that depletes peripheral B lymphocytes, was evaluated for the treatment of calcinosis in 8 articles ranging from case reports, observational studies, and an RCT.[51-59]

Daoussis et al[57] demonstrated a positive outcome measure after 1 year of RTX administration, reporting that the calcific lesions on the knee and elbow had significantly diminished and the associated pain had disappeared. One case report of a patient with SSc-associated myositis with RTX given in 4 weekly infusions (375 mg/m^2) to treat ILD and inflammatory arthritis showed complete resolution of calcinosis in her hands 7 months after the first infusion.[58] In contrast, Poormoghim et al reported a 54-year-old woman with lcSSc and progressive calcinosis cutis, who did not respond to RTX given as 2 infusions at 2-week intervals: 1 g each and 1 g after 6 months.[59] Although generally well tolerated, RTX has been associated with bacterial infection.[54,55]

In the RCT by Aggarwal et al,[56] the primary endpoint was the evaluation of cutaneous activity in adult DM and JDM assessed using the Myositis Disease Activity Assessment Tool, and cutaneous damage including calcinosis using the Myositis Damage Index. Although skin lesions in adult DM and JDM showed

Table 3. Management of calcinosis in rheumatic diseases.

Treatment	Dosage	Study Design	Partial Response, n (%)	Complete Response, n (%)	First Author, Year	No. of Patients (Diseases)	Outcomes
Warfarin	1 mg/d	RCT	0 (0)	0 (0)	Berger, 1987[49,a]	8 (4 placebo; 4 DM, SSc)	No regression of calcinosis
	1 mg/d	R	0 (0)	0 (0)	Lassoued, 1988[50]	6 (DM, SSc)	Worsening of calcinosis, 1 stable
	1 mg/d	R	0 (0)	2 (66)	Cukierman, 2004[51]	3 (SSc)	2 complete regressions of calcinosis
	NA	R	1 (25)	0 (0)	Balin, 2012[44]	4 (SSc, DM)	1 partial response in calcinosis
	NA	R	0 (0)	0 (0)	Fredi, 2015[45]	2 (DM)	No response in calcinotic lesion
Diltiazem	60 mg tid	R	3 (25)	0 (0)	Vayssairat, 1998[8]	12 (SSc)	3 radiographic improvement
	< 480 mg/d	R	9 (53)	0 (0)	Balin, 2012[44]	17 (SSc, DM)	10 cutaneous lesion improvement
	NA	R	0 (0)	0 (0)	Fredi, 2015[45]	12 (DM)	No response in calcinotic lesion
	240-480 mg/d	CS	2 (50)	2 (50)	Palmieri, 1995[42]	4 (CTD)	Regression of calcific lesion
	120 mg bid	CR	NA	1 (100)	Dolan, 1995[43]	1 (SSc)	Remission of calcinosis
	240 mg/d	CR	1 (100)	NA	Farah, 1990[41]	1 (SSc)	Regression of calcinotic lesion
Rituximab	0.575-1 g/m^2 wk 0/1	RCT	NA	1 (14)	Aggarwal, 2017[56,b]	76 (DM), 48 (JDM)	No improvement in calcinosis
	500 mg/m^2 wk 0/2	P	0 (0)	3 (100)	Moazedi-Fuerst, 2015[52]	3 (SSc)	Regression of calcinotic lesion
	500mg/m^2 wk 0/2	P	4 (36)	NA	Narváez, 2014[53]	9 (SSc)	Reduction in calcinotic lesion
	375 mg/m^2/wk × 4	P	3 (50)	NA	Giuggioli, 2015[54]	10 (SSc)	Improvement in calcinosis in 3/6 patients
	2 × 500 mg/m^2	P	0 (0)	0 (0)	Bader-Meunier, 2011[55]	6 (JDM)	No calcinosis improvement in 6 patients
	375 mg/m^2 × 4	CR	NA	1 (100)	Daoussis, 2012[57]	1 (SSc)	Calcinosis significantly improved and pain resolved
Bisphosphonate	NA	R	1 (20)	0 (0)	Balin, 2012[44]	5 (DM, SSc)	1 partial response, 3 had no response
	IV 1 mg/kg/d	R	2 (66)	1 (33)	Marco Puche, 2010[62]	3 (JDM)	Reduction and remission of calcinosis
	IV 1 mg/kg/d	R	2 (33)	2 (33)	Tayfur, 2015[61]	6 (JDM)	Resolution of calcinosis in 4/6 patients
	10 mg/kg/d	CR	1 (100)	NA	Rabens, 1975[64]	1 (SSc)	Partial regression of calcinosis
	10 mg/d	CR	1 (100)	NA	Masza Mukamel, 2001[63]	2 (JDM)	Complete resolution of calcified lesions
	Initial dose 10 mg/kg/d, then 20 mg/kg/d	CR	0 (0)	0 (0)	Metzger, 1974[65]	6 (SSc, DM)	Progression of calcinosis
Surgical excision	NA	R	3 (27)	8 (73)	Balin, 2012[44]	11 (DM, SSc)	Complete response in 8/11 patients
Extracorporeal shock wave lithotripsy	NA	P	4 (100)	0 (0)	Blumhardt, 2016[91]	4 (SSc)	Reduction of calcinosis
	NA	P	1 (33)	0 (0)	Sultan-Bichat, 2012[90]	4 (venous insufficiency), 1 (DM), 3 (SSc)	Reduction of calcinotic lesion
Carbon dioxide laser	P	P	5 (83)	NA	Bottomley, 1996[89]	6 (SSc)	Pain reduction
Iontophoresis of acetic acid	Iontophoresis with 2-5% acetic acid at 10 microA for 20 mins[c]	P	0 (0)	0 (0)	Shetty, 2005[77]	3 (SSc)	Reduction in the intensity of calcinosis in imaging, but no clinical benefits
Surgical excision (microdrilling)	NA	P	12 (80)	NA	Fahmy, 1998[88]	15 (SSc)	Improvement of calcinosis in 12/15 digits

[a] In Berger et al,[49] 4 patients received placebo, 3 received low-dose warfarin, and 1 was excluded for noncomplianace. The outcome was extent of calcinosis based on clinical and radiographic examination. [b] In Aggarwal et al,[56] the primary endpoint was the cutaneous lesions (skin rashes) and not the calcinosis. [c] Iontophoresis was followed by ultrasound at 1.5 W/cm^2 for 8 min occurring 9 times over a 3-week period. Bid: twice daily; CR: case report; CS: case series; CTD: connective tissue diseases; DM: dermatomyositis; IV: intravenous; JDM: juvenile dermatomyositis; NA: not applicable; P: prospective case series; PCT: placebo-controlled trial; R: retrospective case series; RCT: randomized controlled trial; SSc: systemic sclerosis; tid: three times daily.

Table 4. Summary of mechanism of action of therapeutics used to treat calcinosis cutis.

Treatment	Rationale
Warfarin	Warfarin antagonizes vitamin K and therefore reduces the levels of MGP by preventing carboxylation of glutamic acid
Diltiazem	Decrease in the influx of calcium ions into cells leading to correction of an abnormal imbalance of intracellular calcium concentration that may lead to crystal formation
Rituximab	Anti-CD20 antibody that depletes B lymphocytes
Bisphosphonates	Inhibit macrophage proinflammatory cytokine production and reduce calcium turnover
Sodium thiosulfate	Potent antioxidant and vasodilator that also chelates and dissolves calcium deposits
IVIG	Through decreasing inflammation, possibly through inhibition of macrophage function
Minocycline	Tetracycline antibiotic with antiinflammatory and calcium-binding properties
Colchicine	Antiinflammatory effect by disrupting leukocyte chemotaxis and phagocytosis through inhibiting microtubule polymerization

IVIG: intravenous Ig; MGP: matrix gamma-carboxyglutamic acid protein.

improvement after the addition of RTX, there was no significant improvement in calcinosis.[56]

Bisphosphonates. Bisphosphonates have been used based on the rationale that they may be useful in reversing the calcification process by inhibiting macrophage proinflammatory cytokine production and reducing bone resorption.[60] In 3 retrospective cohort studies of 14 individuals,[44,61,62] the efficacy was assessed (Table 3). Another case report conducted on 2 children with JDM stated dramatic improvement in the patient who had dystrophic calcinosis when alendronate was introduced at 10 mg/day to the ongoing therapy.[63] The radiologic changes after 1 year of treatment included an almost complete resolution of the calcified deposition on the axilla along with the active recalcification of the provisional zones of the metaphyses.[63] In a case of severe dystrophic calcinosis and SSc, treated for 1 year with etidronate disodium, the patient had functional improvement and partial resolution of many of the calcified lesions.[64] Conversely, Balin et al[44] found that only 1 of 5 patients had a partial response to bisphosphonate therapy. Also in contrast is a study demonstrating progression of calcinosis with etidronate disodium in 6 patients with dystrophic calcinosis associated with DM and SSc.[65]

Intravenous Ig. The use of IV Ig (IVIG) in the treatment of calcinosis is limited and has shown mixed results. It has been hypothesized that IVIG may have a beneficial effect on calcinosis based on its antiinflammatory properties, possibly related to suppression of activated macrophages. There are conflicting data on evaluating the use of IVIG in SSc-associated calcinosis with positive[66-68] and negative[69] results. In a patient with lcSSc,[70] IVIG (2 g/kg per month) was associated with complete resolution of the symptoms of calcinosis. Further, the calcific lesion was decreased both clinically and radiographically after treatment with IVIG. These results contrast with those reported by Kalajian et al,[69] who described 2 patients with calcinosis associated with DM who had progressive disease despite multiple IVIG cycles.

Sodium thiosulfate. Sodium thiosulfate (STS) is a potent antioxidant and vasodilator that is postulated to chelate and dissolve calcium deposits. Several studies were conducted to assess different regimens of STS or its metabolites. A report describes 2 cases of ulcerative dystrophic calcinosis that had excellent responses to topical 25% STS compounded in zinc oxide.[71] A case series of 1 individual with SSc and 2 individuals with DM showed a significant decrease in size, erythema, and pain with topical 25% sodium metabisulfite (SM). The authors hypothesized that topical SM may dissolve calcium deposits and promote local vasodilation and wound healing.[72] A larger series describes the treatment of 8 lesions in 6 patients (5 with SSc and 1 with nephrogenic systemic fibrosis) with injections. The authors reported the lesions decreased in size, and all patients reported improvement in pain and disability.[73] A report of 3 patients with ACTD-associated calcinosis treated with IV STS did not show any notable clinical improvement of calcinosis (Table 3).[74]

Minocycline. Minocycline (a tetracycline antibiotic) inhibits collagenolytic enzymes including matrix metalloproteinases. Inhibition of these enzymes is important for reducing inflammation and ulceration. In addition, minocycline may also chelate calcium. Robertson et al[75] reported a partial response in 8 of 9 patients treated with minocycline. The most common improvement was a reduction in the incidence of ulceration and inflammation associated with the calcinosis deposits. In addition, reduction in the size of the calcinosis deposits was detected in 1 patient on radiographic examination. However, Balin et al[44] reported a partial improvement in 1 of 6 patients treated with minocycline, with no monitor response using imaging studies; rather, the only detected responses were those described clinically in the patient's medical record. AEs included nausea, dizziness, and conversion of calcinotic cutis deposits to blue/black color.

Acetic acid iontophoresis followed by US. Iontophoresis involves using a small electric current to drive physiologically active ions

(in this case the acetate ion) into the skin. The rationale behind using acetic acid iontophoresis is that the acetate ion replaces the carbonate ion in the insoluble calcium carbonate deposit, forming a more soluble compound, calcium acetate. The US possibly disperses the acetic acid, though there have been studies using US therapy on its own for treatment of calcific deposits.[76] In a small open pilot study, 3 patients with SSc-related calcinosis were subjected to this form of treatment; the outcome measure was the degree of radiographic calcinosis.[77] Even though the mean radiographic intensity of the calcinotic lesions fell in all patients, no patient experienced any clinical improvement. Additional studies are needed to evaluate this potential treatment (Table 3).[77]

Aluminum hydroxide. Aluminum hydroxide interacts with phosphorus, becoming aluminum phosphate, and decreases phosphorus absorption in the intestine. These properties lead to a decrease in the calcification reaction as phosphorus is sequestered into aluminum salts. Oral aluminum hydroxide treatment for calcinosis has been associated with positive responses in SSc[78]; where both symptoms and calcification improved to varying degrees, but there was no complete resolution.

Neem oil with Hypericum *plant extract*. SSc-associated skin ulcers are challenging to treat due to complicating infection or localization of lesions to cutaneous calcinosis. The extracts of *Hypericum perforatum* and *Azadirachta indica* are widely applied in management of skin wounds, eczema, and burns. A study was performed to evaluate the efficacy of a mixture of neem oil (an extract from the fruits and seeds of *A. indica*) and *H. perforatum* for calcinosis-associated ulceration in patients with SSc.[79] The application of the mixture was able to control infection in infected lesions, either by causing progressive crushing and resolution of calcium deposits or easing their sharp excision during wound care. Overall, the diameter of calcinosis-associated ulcers decreased in 27/33 (81.8%) patients with formation of granulation tissue and regularization of margins. Complete healing was reported in 15/33 (45%) patients. A significant improvement (reduction of lesion size, erythema, fibrin, and calcium deposits) was observed for the remaining lesions, and no lesions relapsed during the follow-up period.[79]

Antiinflammatories. Since the pathophysiology of adult and juvenile myositis is the presence of chronic inflammation, prognosis has significantly improved over the last decades with the use of corticosteroids as first-line treatment. Corticosteroids act quickly to stop the disease process. Different corticosteroid regimes have been proposed for the initial treatment of JDM, with the most-reported use being oral prednisolone or prednisone in a dose of 2 mg/kg/day and pulses with IV methylprednisolone (MP) 30 mg/kg/day followed by oral prednisone. A comparative study[80] failed to demonstrate superiority of 1 regime over the other in the presence of calcinosis, whereas other reports[81,82] suggested that residual weakness, relapsing disease, and calcinosis are lower in patients receiving pulse IV rather than oral therapy. Moreover, a study published in 2000 suggested that IV MP, although more costly, may potentially be cost effective when compared to oral corticosteroids.[83] The significant antiinflammatory effects of corticosteroids cannot, however, be separated from their metabolic effects, particularly the effects on growth, immunity, and adrenal suppression.

Treprostinil. The safety and efficacy of oral treprostinil in preventing progression of SSc-associated calcinosis was evaluated.[84] Twelve female patients with SSc were enrolled, with confirmed clinical and radiographic evidence of ≥ 1 calcinosis deposit in the hands. Patients received oral treprostinil for 1 year. Primary endpoints were safety and tolerability and percentage of patients without radiographic progression of calcinosis at 1 year. Five patients completed the study. Seven patients withdrew due to intolerable AEs, intercurrent unrelated illness, progressive SSc, and personal reasons. Most patients developed headaches and gastrointestinal AEs. Four of 11 (36%) patients with 1-year follow-up hand radiographs experienced progression of calcinosis. Of 5 who completed treatment, calcinosis was stable in 4 (80%) patients with progression in 1 patient.[84]

Tofacitinib. In DM, type I interferon contributes to pathophysiology by inducing the expression of proinflammatory cytokines, and the Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway is involved in cutaneous manifestations of DM.[85] STAT3 is able to translocate into mitochondria and may be involved in the regulation of mitochondrial calcium store release, a process potentially important for calcification in DM. Based on these findings, JAK inhibitors (JAKi) that can interfere with recruitment of STATs and downregulate type I and II cytokine signaling, can be considered in DM therapy. Two patients with severely calcifying DM were treated with JAKi (tofacitinib [TOF]).[86] A female patient who presented with rapid progressive muscular and subcutaneous calcifications in both hands, resulting in complete functional disability, was given TOF therapy (5 mg bid) in combination with methotrexate (12.5 mg/week) and prednisone (5 mg/day). After 28 weeks, inflammation due to calcifications had completely resolved, calcifications were either stable or regressed, acral ulcers had disappeared, and functional status had further improved. The second case was a female patient with DM-associated ILD in whom calcifications failed to respond to the regular treatment regimen. TOF monotherapy (5 mg bid) was started and after 28 weeks, reports showed no new calcifications had formed and some calcifications had even further improved, while others remained unchanged. No side effects occurred during TOF treatment, except for an increase in bodyweight.[86]

Nonpharmacologic interventions

We may consider nonpharmacologic interventions in selected patients. Nonpharmacologic interventions are usually reserved for specific index lesions that are significantly symptomatic, for example, causing chronic pain, dyspareunia, or compression neuropathy. Interventions may include surgical excision, carbon dioxide laser, and extracorporeal shock wave lithotripsy.

Surgical excision. Patients with large, localized, symptomatic lesions, located over tendons, blood vessels, and nerves, are referred for surgery. Surgical excision has not been considered an optimal therapeutic option due to the increased risk of slowed wound healing, infection, and possibly decreased range

of motion. Surgical treatment is not always an option due to the size of the calcinotic lesion, the extent of tissue involvement and/or the number of lesions. In a review of hand surgery studies for SSc, Bogoch and Gross[87] found that, of 13 reports evaluating calcinosis cutis, studies reported an improvement of pain and functional outcomes. Balin et al[44] reported that all 11 patients who received surgical excision alone responded, with 8 having a complete response and 3 patients having partial response (Table 3). Balin et al considered total resolution of an individual lesion and lack of recurrence in that area as a complete response, while regression or recurrence of a lesion that had previously regressed or completely healed as a partial response.[44] The persistence of old lesions with or without the occurrence of new lesions indicated no response. An alternative option is the use of a high-speed dental burr instead of a scalpel, which may lead to better results,[88] as wound healing is faster and patients may experience improvement in pain and function.

Carbon dioxide laser. Carbon dioxide (CO_2) laser has been widely and successfully used in surgery. It provides a relatively bloodless field to the surgeon; it is precise and causes less damage to surrounding healthy tissues. The CO_2 laser has been used to "vaporize" superficial calcinosis. In 1 prospective study, CO_2 laser was found to be effective in treating 6 patients with lcSSc with digital calcinosis cutis.[89] Lesions were evaluated and treated in 21 sites; complete resolution was seen in 12 areas, moderate response in 5, minor response in 2, and recurrence of calcinosis in another 2. Procedure-related infections were seen in 2 patients, which resolved completely with antibiotic treatment (Table 3).[89]

Extracorporeal shock wave lithotripsy. Extracorporeal shock wave lithotripsy (ESWL) is a minimally invasive procedure where acoustic shock waves are used to break apart mineral deposits, in principle destroying calcifications. It has a high success rate and low morbidity and is widely used in the treatment of nephrolithiasis and calcific tendinitis. A prospective study of 9 patients (3 with SSc) with calcinosis found that 3 ESWL sessions at 3-week intervals reduced the size and pain from calcinosis at 6 months.[90] A 12-week study of 3 weekly sessions of ESWL on calcinosis lesions in 4 patients with SSc found a reduction in lesion size in 3 patients and pain improvement in 2 patients.[90,91] ESWL showed effectiveness in the treatment of calcinosis cutis (Table 3).

Conclusion

In summary, calcinosis is an important manifestation of several SARDs. Although infrequent in the general RD population, calcinosis can result in significant morbidity and impair quality of life among those who suffer from it. It is a clinical challenge for rheumatologists who care for these patients. In this article, we have outlined our approach to the management of calcinosis. We summarized the current evidence for pharmacologic and nonpharmacologic interventions for your consideration in the care of these patients.

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