Management of calcinosis cutis in rheumatic diseases

Hadiya Elahmar, Brian M. Feldman, Sindhu R Johnson

Hadiya Elahmar MD, Dermatologist at U-turn Dermatology Clinic, Kuwait; Dermatology and Venerology, Ain Shams University, Cairo, Egypt.

Brian M Feldman MD MSc, Pediatrics, Medicine, Institute of Health Policy Management and Evaluation, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada.

Sindhu R Johnson MD PhD, Toronto Scleroderma Program, Mount Sinai Hospital, Toronto Western Hospital, Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. Orcid ID 0000-0003-0591-2976.

Corresponding Author. Dr. Sindhu Johnson, Division of Rheumatology, Ground Floor, East Wing, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada, M5T 2S8. Phone 1-416-603-6417 Fax.1-416-603-4348. Email: Sindhu.Johnson@uhn.ca
Twitter @SindhuJohnson5

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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 non-pharmacologic and pharmacologic interventions for the treatment of calcinosis.

Introduction

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 paediatric systemic autoimmune rheumatic diseases. The most frequent rheumatic diseases 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 rheumatic diseases. In this article, we outline our approach to the evaluation, diagnosis and management of calcinosis. We summarize the evidence supporting pharmacologic interventions and non-pharmacologic treatments for calcinosis.

Current understanding of calcinosis in rheumatic diseases

Classification. Boulmann *et al*(5) classified the soft tissue classification into five subtypes: dystrophic, metastatic, idiopathic, tumoral and calciphylaxis (Table 2). Systemic autoimmune rheumatic diseases 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). (Figures 1 and 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 lcSSc and 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 limited cutaneous SSc. For example, a large cohort found an increased risk of calcinosis in diffuse cutaneous SSc patients 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, osteoporosis, internal organ involvement, specifically interstitial lung disease (ILD)(16, 17). Calcinosis is a long-term, debilitating manifestation of these diseases which adversely impacts 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 and up to 20-40% in juvenile dermatomyositis(6). Calcinosis cutis typically arises within 2–3 years from the onset of juvenile dermatomyositis, which is faster than it occurs with other connective tissue disorders or adult dermatomyositis, which has an average onset of calcinosis cutis at approximately 8 years(24). In juvenile DM, the most common antibodies are anti-TIF-1γ in 18% of the children, followed by anti-NXP-2 (15%) and anti-MDA-5 (6%).(25) Anti-NXP-2 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 and juvenile dermatomyositis; whereas anti-TIF-1 is associated with a decreased risk of calcinosis in adult dermatomyositis.(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-1, interlukin-6, interlukin-1b and tumour necrosis factor (TNF), supports the role of inflammation in calcinosis development. Evidence demonstrated by Davis *et al*, suggested an increased expression of hypoxia-associated glucose transporter molecule (GLUT-1) in skin biopsies of SSc patients with calcinosis(27), contributing to the vascular ischemic theory. (Table 1) Studies also reported elevated vascular endothelial growth factor (VEGF) levels, a potent angiogenic factor induced by hypoxia, associated with increased osteoclast activity in SSc patients with calcinosis(28), suggesting hypoxia-induced imbalance between angiogenic factors (such as VEGF, platelet derived growth factors) and antiangiogenic factors (such as angiostatin, 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 development of calcinosis (Table 1) possibly explaining the association between calcinosis and osteoporosis.(10, 13, 29)

Additionally, a frequent history of digital ulcers(11, 30) can be related to the vascular hypoxia and recurrent trauma hypotheses, with or without acro-osteolysis.(16, 17) (Table 1)
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 SSc patients. 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 under-gamma-carboxylated and inactive MGP, causing dysregulated calcification.(32) (Table 1)

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 few millimetres 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 hips (6.7%).(7, 14) Figure 1. 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), the metacarpophalangeal or the interphalangeal joints.

In dermatomyositis associated with calcinosis, the affected areas include the extremities and trunk. Calcinosis can also develop in areas that were previously involved by the dermatomyositis process, which may include muscle calcification. Dystrophic calcification in dermatomyositis appears as small, localized nodules or papules, subcutaneous tumoral deposits, or intramuscular and fascial calcification sometimes leading to an exoskeleton formation which 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 is 89%

sensitive in the detection of calcinosis(35). Further experimental modalities include multidetector computed tomography (MDCT), dual-energy computed tomography (DECT) and magnetic resonance imaging (MRI). Favourably, MDCT provides a higher resolution and 3D images for a better assessment(36). Recently a radiographic scoring system(37) was developed to standardise the measurement of calcium deposits for hand calcinosis. Another method categorizes lesions accordingly to the radiographic shape, pattern of lesions and clinical appearances as four subtypes: mousse, stone, net and plate(14).

Recommended approach for the management of calcinosis

General measures

There is no cure for calcinosis, and it remains a therapeutic challenge in patients with rheumatic diseases. We do not treat asymptomatic calcinosis pharmacologically. General measures include avoiding trauma, and measures to improve blood flow to the extremities such as avoiding smoking, and exposure to the cold and stress. Treatment of Raynaud's phenomenon and digital ulcers 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 (e.g., Polysporin complete) may treat minor soft tissue infection and relieve pain. Oral broad-spectrum antibiotics are required for moderate soft tissue infection whereas intravenous antibiotics are required for progressive soft tissue infection or involvement of a tendon sheath. Non-steroidal anti-inflammatory 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 juvenile dermatomyositis, 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 improves 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, cochicine, 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 are 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 (ACTD) studied to date. Diltiazem was effective in nine 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 were found.(8) Similarly, no complete response was reported in a retrospective cohort study by Fredi *et al*.(45)

Colchicine. Colchicine has an anti-inflammatory effect by disturbing leukocyte chemotaxis and phagocytosis through inhibiting microtubule polymerization. In a patient with dermatomyositis and a patient with SSc-associated calcinosis cutis, oral colchicine at a dose of 1 mg/d 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 eight calcinosis patients treated with colchicine found that three responded positively, with one 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. (Table 3)

Warfarin. Warfarin, a vitamin k antagonist, has been proposed for treatment of calcinosis, based on the rationale that it reduces the levels of Matrix Gla protein (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 under-carboxylated MGP.(47, 48) Warfarin was evaluated in one randomized controlled trial(49) and retrospective cohort studies.(44, 45, 50, 51) In a study by Cukierman et al, 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. Balin *et al* (44) demonstrated that four 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 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 extra-skeletal uptake on technetium 99m-diphosphonate whole-body nuclear scanning and decreased gamma-carboxyglutamic acid urinary concentration. Similarly, Lassoued et al reported a small cohort study evaluating the effect of warfarin treatment on extent of calcinosis based on clinical and radiographic (plain radiographs or computerized tomography) examination. They too found no clinical improvement in 5 patients (one with SSc) with extensive and long standing calcinosis treated with low-dose warfarin.(50) All 5 patients had clinical and radiological worsening of calcinosis. The range of responses are illustrated in Table 3 and proposed mechanisms in Table 4.

Rituximab. The use of rituximab, a monoclonal anti-CD20 antibody that depletes peripheral B lymphocytes, was evaluated for the treatment of calcinosis in 7 studies including 4 prospective cohort studies (52-55), and a randomized control trial.(56) (Table 3) Daoussis *et al*.(57) demonstrated a positive outcome measure after 1 year of rituximab administration, reporting 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-

myositis with rituximab given in four weekly infusions (375 mg/m2) to treat interstitial lung disease and arthritis showed complete resolution of calcinosis in her hands 7 months after the first infusion.(58) In contrast, Poormoghim *et al.* stated a 54-year-old lady, with limited cutaneous scleroderma and progressive calcinosis cutis, did not respond to rituximab given as two infusions at 2-week intervals, 1 g each and 1g after 6months. (59) Adverse events were recorded in 3 studies that included bacterial infection and intestinal perforation after combination of rituximab with pulse methylprednisolone infusions.

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 improvement after the addition of rituximab 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 17 individuals (44, 61, 62), the efficacy was assessed (Table 3). Another case report conducted on 2 children with juvenile dermatomyositis stated dramatic improvement in the patient who had dystrophic calcinosis when alendronate was introduced at 10mg/day to the ongoing therapy. 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 one of five patients had a partial response to bisphosphonate therapy. Also in contrast is

a study demonstrating progression of calcinosis with etidronate disodium in six patients with dystrophic calcinosis associated with dermatomyositis and SSc.(65)

Intravenous immunoglobulins. The use of intravenous immunoglobulins (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 anti-inflammatory 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 limited cutaneous SSc(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 those reported by Kalajian *et al*(69) who described two patients with calcinosis associated with dermatomyositis who had progressive disease despite multiple IVIg cycles. (Table 3).

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 two cases of ulcerative dystrophic calcinosis that had excellent responses to topical 25% STS compounded in zinc oxide.(71) Four patients with calcinosis (one with SSc and two with dermatomyositis) 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 eight lesions in six patients (five with SSc and one with nephrogenic systemic fibrosis) with injections; the lesions decreased in size by 67% and 90%, respectively, and all patients reported improved pain and disability.(73) A report of three patients with ACTD-

associated calcinosis treated with intravenous STS, did not show any notable clinical improvement of calcinosis.(74) (Table 3).

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 8/9 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 one patient on x-ray examination. However, Balin *et al.*(44) reported a partial response in 1/3, with no monitor response using imaging studies; rather, the only detected responses were those described clinically in the patient's medical record. (Table 3). Adverse effects included nausea, dizziness, and conversion of calcinotic cutis deposits to blue/black colour.

Acetic acid iontophoresis followed by ultrasound. 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 ultrasound possibly disperses the acetic acid, though there have been studies using ultrasound therapy on its own for treatment of calcific deposits.(76) In a small open pilot study, three patients with SSc-related calcinosis were subjected to this form of treatment; the outcome measure was the degree of radiographic calcinosis. 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.(77) (Table 3)

Aluminium hydroxide. Aluminium hydroxide interacts with phosphorus, becoming aluminium phosphate, and decreases phosphorus absorption in the intestine. These properties lead to a decrease in the calcification reaction as phosphorus is sequestered into aluminium salts. Oral aluminium hydroxide has been evaluated in calcinosis associated with positive responses in SSc(78), both symptoms and calcification resolved 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 Azadirachta indica) and Hypericum perforatum, for calcinosis associated ulceration in SSc patients. The application of the mixture was able to control infection in infected lesions, either by causing progressive crushing and resolution of calcium deposits or eased 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 (45.4%) 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)

Anti-inflammatories. 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 used being oral prednisolone or prednisone in a dose of 2 mg/kg/day and pulses with intravenous methylprednisolone (IV MP) 30mg/kg/day followed by oral prednisone. A comparative study(80) failed to demonstrate superiority of one regime over the other in the presence of calcinosis, while other reports(81, 82) suggested that residual weakness, relapsing disease and calcinosis are lower in patients receiving pulse intravenous rather than oral therapy. Moreover, a study published in 2000(83) suggested that IV MP although more costly, may potentially be cost effective when compared to oral corticosteroids. The significant anti-inflammatory 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. Twelve female SSc patients 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/tolerability and percentage of patients without radiographic progression of calcinosis at 1 year. Five patients completed the study. Seven patients withdrew due to intolerable adverse effects, intercurrent unrelated illness, progressive SSc, and personal reasons. Most patients developed headaches and gastrointestinal adverse effects. 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 1patient.(84)

Tofacitinib. In DM, type I interferon contributes to pathophysiology by inducing the expression of proinflammatory cytokines and the JAK-STAT (signal transducer and activator of transcription) 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 (JAK-I) that can interfere with recruitment of STATs and downregulate type I and II cytokine signalling, can be considered in DM therapy. Two patients with severely calcifying dermatomyositis were treated with the JAK-I (tofacitinib). A female patient presented with rapid progressive muscular and subcutaneous calcifications in both hands resulting in complete functional disability was given the tofacitinib therapy (5 mg twice daily) in combination with methotrexate (12.5 mg/week) and prednisone (5 mg/day). After 28 weeks, inflammation of calcifications had completely resolved, and calcifications were either stable or regressive, acral ulcers had disappeared and the functional manual status had further improved. The 2nd case was a female patient with DM associated interstitial lung disease and calcifications failed to respond to the regular treatment regimen. Tofacitinib monotherapy (5 mg twice/day) was started and after 28 weeks reports showed no new calcifications had formed, some calcifications had even further improved, while others remained unchanged. No side effects occurred during tofacitinib treatment except for an increase in bodyweight.(86)

Non-Pharmacologic Interventions

We may consider non-pharmacologic interventions in selected patients. Non-pharmacologic 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 applicable given the size and extent of tissue involvement, and number of lesions. In a review of hand surgery studies for systemic sclerosis Bogoch and Gross(87) found that, of 13 reports evaluating calcinosis cutis, studies reported an improvement of pain and functional outcomes. Balin *et al*. reported 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. 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 (CO_2 laser). 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 CO2 laser has been used to "vaporize" superficial calcinosis. In one prospective study, CO2 laser has been found to be effective in treating 6 limited cutaneous SSc with digital calcinosis cutis. 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 two. Procedure-related infections were seen in 2 patients, which resolved completely with antibiotic treatment.(89) (Table 3)

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 nine patients (three with SSc) with calcinosis found that three ESWL sessions at 3-week intervals reduced the size and pain from calcinosis at 6 months. A 12-week study of three weekly sessions of ESWL on calcinosis lesions in four SSc patients found a reduction in lesion size in three patients and pain improvement in two patients.(90, 91) ESWL showed effectiveness in the treatment of calcinosis cutis. (Table 3)

In summary, calcinosis is an important manifestation of several systemic autoimmune rheumatic diseases. Although infrequent in the general rheumatic disease 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 summarize the current evidence for pharmacologic and non-pharmacologic interventions for your consideration in the care of these patients.

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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.

Table 1. 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 anti-angiogenic factors (such as angiostatin, endostatin) Increased expression of the hypoxia-associated glucose transporter molecule (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

Table 2. 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	Normal	Tumoral calcinosis Calcified subepidermal	Multiple, asymptomatic nodules, which

	or metabolic disturbances		nodules (nodular calcinosis of Winer) Scrotal calcinosis	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

Table 3. Management of calcinosis in rheumatic diseases.

Treatment	Dosage	Study design	Partial response, N (%)	Complete response, N (%)	Reference	Number of patients (Diseases)	Outcomes
Warfarin	1mg/day	RCT	0 (0%)	0 (0%)	Berger *et al. 1987**	8 (4 placebo,4 DM, SSc)	No regression of calcinosis
	1mg/day	R	0 (0%)	0 (0%)	Lassoued *et al. 1988*	6 patient DM, SSc	Worsening of calcinosis, 1 stable
	1mg/day	R	0 (0%)	2 (66%)	Cukiermann *et al. 2004*	3 SSc	2 complete regressions of calcinosis
	NA	R	1 (25%)	0 (0%)	Balin *et al. 2012*	4 SSc, DM	1 partial response in calcinosis
	NA	R	0 (0%)	0 (0%)	Fredi *et al. 2015*	2 DM	No response in calcinotic lesion
Diltiazem	60 mg x3/day	R	3 (25%)	0 (0%)	Vayssairat *et al. 1998*	12 SSc	3 radiographic improvement
	<480 mg/day	R	9 (53%)	0 (0%)	Balin *et al. 2012*	17 SSc, DM	10 improve cutaneous lesion
	NA	R	0 (0%)	0 (0%)	Fredi *et al. 2015*	12 DM	No response in calcinotic lesion
	240-480mg/day	Case series	2 (50%)	2 (50%)	Palmieri *et al. 1995*	4 CTD	Regression of calcific lesion
	120mg BID	Case report	NA	1 (100%)	Dolan *et al. 1995*	1 SSc	Remission of calcinosis
	240 mg daily	Case report	1(100%)	NA	Farah *et al. 1990*	1SSc	Regression of calcinotic lesion
Rituximab	0.575-1g/m2 week0/1	RCT	NA	1 (14%)	Aggarwal *et al. 2016***	76 DM, 48 JDM	No improvement in calcinosis
	500mg/m2 week0/2	P	2 (40%)	3 (60%)	Moazedi *et al. 2015*	5 SSc	Regression of calcinotic lesion
	NA	P	NA	4 (50%)	Narvaez *et al. 2014*	9 SSc	Reduction in calcinotic lesion
	375mg/m2weeklyx4	P	3 (50%)	NA	Giuggioli *et al. 2015*	10 SSc	Improved extent of skin sclerosis
	375mg/m2weeklyx4	Case report	NA	1 (100%)	De Paula *et al.* 2012	1 SSc	Complete resolution of calcinosis
	2x500mg/m2	P	0 (0%)	0 (0%)	Bader *et al. 2011*	9 JDM	No calcinosis improvement in 6 patients, but 3 complete clinical response
	4x375mg/m2 2 courses 4 weekly infusions, 375 mg/m2 each)	Case report	NA	1 (100%)	Daoussis *et al. 2012*	1 SSc	Calcinosis significantly improved and pain resolved
Bisphosphonate	NA	R	1 (20%)	0 (0%)	Balin *et al. 2012*	5 DM, SSc	1 partial response, 3 had no response
	IV 1mg/kg/day	R	2 (66%)	1 (33%)	Marco *et al. 2009*	3 JDM	Reduction and remission of calcinosis
	IV 1mg/kg/day	R	2(33%)	2(33%)	Tayfur *et al. 2015*	6 JDM	Resolution of calcinosis in 4/6 patients
	10mg/kg/day	Case report	1(100%	NA	Rabens *et al. 1975*	1 SSc	Partial regression of calcinosis
	10mg/day	Case report	1(100%	NA	Mukamel *et al*. 2001	2 JDM	Complete resolution of calcified lesions
	Initial dose 10mg/kg/day then 20mg/kg/day	Case series	0 (0%)	0 (0%)	Metzger *et al. 1974*	3DM, 3JDM	Progression of calcinosis
Surgical excision		R	5 (18%)	22(79%)	Balin *et al. 2012*	11 DM, SSc	8 complete remissions of calcinotic lesion
Extracorporeal shock wave lithotripsy		P	4(100%)	0 (0%)	Blumhardt *et al. 2016*	SSc	Reduction of calcinosis
			1 (33%)	0 (0%)	Sultan *et al. 2012*	4 venous insufficiency, 1 DM, 3 SSc	Reduction of calcinotic lesion
Carbon dioxide laser		P	5 (83%)	NA	Bottomley *et al. 1996*	6 SSc	Pain reduction

Iontophoresis of acetic acid and ultrasound	P	0 (0%)	0 (0%)	Shetty *2005*	3 SSc	Reduction in the intensity of calcinosis in imaging, but no clinical benefits
Surgical excision (micro-drilling)	P	12(80%)	NA	Fahmy 1998	15 SSc	Improvement calcinosis in 12/15 digits

R: Retrospective case series, P: Prospective case series, RCT: Randomized controlled trial, PCT: Placebo controlled trial.
*****In *Berger et al.* 4 patients received placebo, 3 received low dose warfarin and 1 was excluded for non-complianace. The outcome was extent of calcinosis based on clinical and radiographic examination.
****** In Aggarwal et al, the primary endpoint was the cutaneous lesions (skin rashes) and not the calcinosis.

SSc Systemic sclerosis, DM Dermatomyositis, JDM Juvenile Dermatomyositis, CTD Connective Tissue Diseases

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	By inhibiting macrophage proinflammatory cytokine production and reduce calcium turnover.
Sodium thiosulfate	Potent antioxidant and vasodilator that also chelates and dissolves calcium deposits.
Intravenous immunoglobulin	Through decreasing inflammation, possibly through inhibition of macrophage function.
Minocycline	Tetracycline antibiotic with anti-inflammatory and calcium-binding properties

Colchicine	Anti-inflammatory effect by disrupting leukocyte chemotaxis and phagocytosis through inhibiting microtubule polymerization

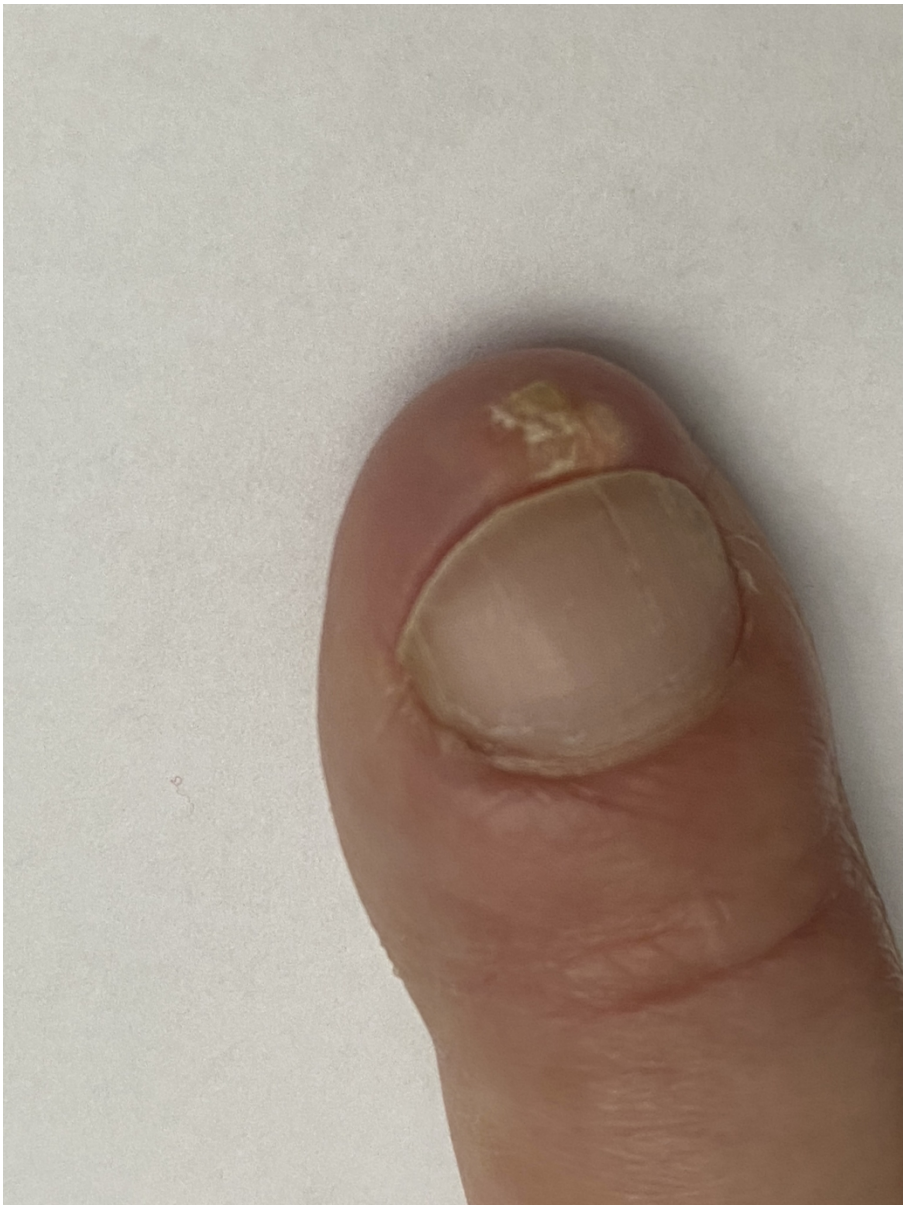

Figure 1. Calcinosis cutis in the soft tissue at the tip of the finger

1066x1422mm (72 x 72 DPI)

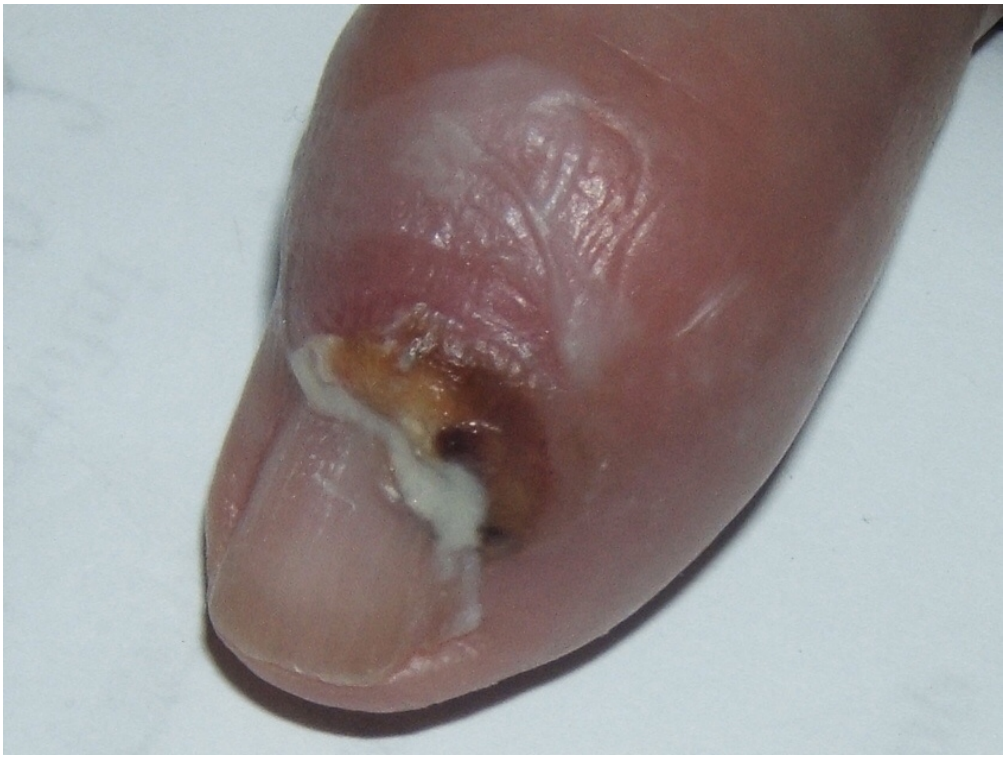

Figure 2. Liquified calcinosis draining from the soft tissue proximal to the fingernail.

297x222mm (72 x 72 DPI)