

# Calcinosis in Juvenile Dermatomyositis: Pathogenesis and Current Therapies

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**Abstract.**

Calcinosis is one of the hallmark sequelae of juvenile dermatomyositis, and despite recent progress in the therapy of these disorders, dystrophic calcification still occurs in approximately one-third of patients. This review discusses our current, albeit limited, understanding of risk factors for the development of calcinosis in juvenile dermatomyositis, as well as current views on its pathogenesis. Anecdotal approaches to treating calcinosis associated with juvenile dermatomyositis, including both anti-inflammatory therapies and agents aimed at inhibiting the deposition of calcium hydroxyapatite are reviewed. An improved understanding of the pathogenesis of calcinosis, as well as randomized controlled trials employing more sensitive outcome measures should aid in developing efficacious therapies for this often disabling complication.

Juvenile dermatomyositis (JDM) is a rare systemic connective tissue disease characterized by muscle weakness and chronic muscle inflammation of unknown etiology (1). Two skin rashes, Gottron's papules and heliotrope rash, are pathognomonic and assist in confirming the diagnosis. The disease has a number of protean manifestations, but calcinosis is the sequelae that is perhaps most characteristic for this illness, most troublesome, and least understood.

Calcinosis occurs in up to 30% of patients with JDM, although current prevalence ranges from 10 – 50% (2-5). Despite recent considerations that the frequency has been declining, this is not currently clear. The calcification is dystrophic, which by definition occurs at sites of injured tissue with simultaneously generally normal serum calcium and phosphorous levels (6). The sites most frequently affected are the elbows, knees, digits and extremities, although it may occur virtually anywhere over the body (7). The onset of calcinosis is most often 1 – 3 years after illness onset, but has been reported to occur from the time of illness onset to as long as 20 years later (8). Prior to therapy with corticosteroids, when mortality exceeded 50%, the development of calcinosis was a good prognostic sign; today, it is a marker of disease morbidity and possibly inadequate treatment.

Four subtypes of dystrophic calcification have been recognized in the dermatological literature, and these have been described in JDM as well (9). In one large series (5), 33% of patients developed superficial plaques or nodules (calcinosis circumscripta), which are small nodules confined to the skin or subcutaneous tissue.[\(Figure 1a\)](#) Twenty percent of patients in this series developed tumoral calcinosis (also known as calcinosis universalis), which are larger nodular deposits that may extend to deeper tissue layers, including the muscle.[\(Figure 1b\)](#) Calcinosis along fascial planes of muscles and tendons was observed in 16% of patients [\(Figure 1c\)](#), and exoskeleton, an extensive hard calcium deposition over all body surface areas, was seen in 10%.[\(Figure 1d\)](#) Twenty-two percent had a mixture of calcinosis subtypes.

Our current understanding of risk factors for the development of calcinosis is limited and based largely on small, retrospective series of patients. Calcinosis has been associated with a delay to diagnosis and initiation of appropriate therapy for JDM, and this association is strengthened by prospective data from a large registry of new-onset cases (3,10). Patients receiving an inadequate initial course of corticosteroid therapy (< 2 mg/kg/day) that is also delayed more than 4 months after first symptoms of illness develop calcinosis in greater proportion (65%) than those in which a higher daily dose of corticosteroid is initiated without a delay to diagnosis (37%) (5). Patients with a chronic or polycyclic illness course, as well as those with a longer duration of active disease, may be more likely to develop calcinosis (3,11).

The subtype of calcinosis may also be related to disease severity, with the exoskeleton subtype particularly associated with a chronic illness course (5) and severe disease associated with fascial plane deposition (7). Patients with calcinosis may have lower antinuclear antibody titers, although calcinosis is one of the clinical features associated with the myositis-associated

autoantibody PM-Scl (11,12). Patients with a low initial creatine kinase level develop calcinosis less frequently (13), whereas patients with a longer duration of elevated muscle enzymes are more likely to develop calcinosis (3). Finally, patients who develop lipodystrophy as a complication of JDM frequently have calcinosis (14).

Two multi-center studies found no relationship between the development of calcinosis and age at diagnosis, gender, race, disease severity at onset, presence of ulcerations, or center at which the patient received treatment (4,11). In summary, longstanding active disease in which there is a delay to appropriate initial therapy or an inadequate course of treatment appears to be most associated with the development of calcinosis.

Calcinosis is associated with a variable natural history and a number of sequelae in children with JDM. Over an unpredictable period of time, spontaneous regression, either through re-absorption or extrusion of the material, may occur (7,15). Improvement in calcinosis may be more likely in patients with inactive disease, those engaging in a lot of physical activity, those with superficial plaques or nodules rather than with deeper or more extensive deposits, and those treated with an aggressive therapeutic regimen for JDM. Alternatively, the calcinosis may not change over time, or even progress. In our experience, progression is more likely when there is ongoing, inadequately treated myositis disease activity.

Because the lesions often cross joint margins, joint contractures may result. JDM patients with calcinosis have also had higher levels of functional disability than those without (4). Many JDM patients with calcinosis develop an inflammatory reaction during active deposition of the lesion, which can result in erythema, tenderness and drainage over the site, but systemic manifestations such as fever may also be present. It is important to distinguish this reaction from an actual cellulitis, which requires antimicrobial therapy for *Staphylococcus aureus*, and which can be associated with increased serum IgE levels and diminished polymorphonuclear leukocyte chemotaxis (16,17). Tumoral calcinosis lesions can also develop ulceration of the overlying skin (5,7). When there is nerve entrapment or a pressure point is involved, pain may be a major complication (18). For all patients with calcinosis, physical disfigurement and a resulting psychological impairment are present.

Our understanding of the pathogenesis of calcinosis is very limited, but has recently begun to come into focus based on anecdotal reports. A growing body of data is accumulating that supports our understanding of other calcification processes, such as intimal calcification seen in atherosclerosis or cardiac valve calcification (19-21). Although these studies have some potential applicability to JDM, there are important differences in these processes compared to the calcinosis of JDM, including the fact that they result in new bone formation, whereas the calcification associated with JDM generally does not.

Anecdotally, JDM patients with tissue injuries following minor trauma appear to develop calcinosis at the injured sites, particularly when the underlying myositis is still active. Our

experience at the NIH includes patients developing calcinosis in the medial thigh with repetitive horseback riding, as well as along the humerus after being pulled when walking a dog; and a patient who developed a hematoma following a surgical muscle biopsy procedure and subsequent calcinosis at the same site. Tissue injury and hematoma formation have been associated with other dystrophic calcification processes (6).

The calcinosis itself is also associated with inflammation. In a recent report by Mukamel et al., macrophages and pro-inflammatory cytokines, including IL-6, IL-1 and TNF- $\alpha$ , were present in the milk of calcium fluid examined from a patient (22). Calcinosis has also been more frequently associated with the TNF- $\alpha$  -308A promoter polymorphism, which is associated with increased TNF- $\alpha$  production by peripheral blood mononuclear cells (23). It is likely there are other predisposing genetic risk factors that have not yet been discovered. Our group has also observed that new-onset calcinosis is associated with subcutaneous edema in the same location, which is presumed to be inflammation, on a short tau inversion recovery (STIR) magnetic resonance imaging exam (24).

The histopathology of surgically-removed specimens, often of longstanding duration, demonstrate chronic inflammatory cells encapsulating the mineral consisting apparently of a variety of cell types, including possibly macrophages, giant cells, lymphocytes and eosinophils (25-27). In most studies, there is no apparent bone formation, with no evidence of osteoblasts, osteoclasts, osteocytes or ossification centers, or these occur as a secondary process (26). The calcium mineral itself may be a chemoattractant for macrophages and monocytes (28). Preliminary x-ray diffraction studies suggest the mineral is calcium hydroxyapatite (25,26).

Finally, several reports have demonstrated connective tissue and mineral-associated proteins in calcinosis lesions and JDM muscle tissue. The deposited calcium appears to be nucleated around collagen and elastic fibers (29). Gla protein (osteocalcin), a connective tissue protein, has been reported to be present in the calcinosis tissue from one JDM patient, and its urinary excretion is increased in JDM patients (although this may be confounded by corticosteroid use) (30,31). Other mineralization matrix proteins, including bone sialoprotein, bone acidic glycoprotein 75 and osteopontin, are expressed in very active JDM muscle tissue (23). These proteins, likely upregulated in expression by tissue macrophages, cytokines and tissue injury, may serve as a nidus for nucleation of the mineralized calcium that would then promote crystal growth (32,33). Some of these proteins may initiate or promote mineralization, whereas others apparently inhibit hydroxyapatite crystal growth. Osteopontin apparently not only inhibits mineral deposition, but also actively promotes its dissolution by inducing expression of carbonic anhydrase in monocytes and promoting acidification of the extracellular environment (34). A balance of pro-mineralizing matrix proteins would favor growth of existing lesions and further deposition of new lesions.

Figure 2 provides a hypothesis of the pathogenesis of calcinosis in JDM, based on these limited data, providing a central role in the cascade for the associated inflammatory process.

Current approaches to the treatment of calcinosis associated with JDM are based largely on anecdotal reports, with only one controlled therapeutic trial ever performed. One of the major difficulties in the interpretation of these uncontrolled studies is that the natural history of these lesions is unpredictable and spontaneous regression may occur. The reports generally do not clarify how active the myositis is or what stage the calcinosis is (actively depositing vs. present for long duration). Case reports of ineffective therapies often result in a potential treatment approach being discarded, but these are also often plagued by inadequate dosage or trial duration. Many of the outcome measures used to assess therapeutic responses have been insensitive, based on a clinical examination or plain radiography or scintigraphy (35). Scintigraphy, for example, may not detect all calcinosis lesions, and thin section CT scanning appears to be much more sensitive in detecting earlier lesions, because of the sensitive bone-water interface (36). Finally, patients and physicians often are unrealistic in their therapeutic expectations: they desire resolution of calcinosis in a short period of time following the initiation of an agent, whereas retardation of progression over a longer period of time is a more appropriate therapeutic aim. There is a great need to not only develop sensitive outcome measures to examine the efficacy of agents in treating calcinosis, but also to conduct randomized, controlled trials of agents in order to appropriately test their efficacy.

Prior to treating existing calcinosis, the first aim of therapy in patients with JDM is to prevent the development of calcinosis. Three recent reports suggest that the early initiation of intensive anti-inflammatory therapy for JDM may be effective in preventing future development of calcinosis. In a retrospective study, repetitive intravenous pulse methylprednisolone therapy (30 mg/kg/dose, with the number of doses titrated to each individual patient's response) as initial therapy for JDM resulted in no calcinosis compared to oral prednisone alone, which resulted in the development of calcinosis in 34% of patients (37). Intermittent intravenous pulse methylprednisolone, followed by oral corticosteroids and early introduction of methotrexate within 6 weeks of diagnosis also results in either no calcinosis or a low frequency of calcinosis, compared to later introduction of methotrexate in which the frequency of calcinosis is comparable to that of historical rates (3,38).

For patients who are actively depositing calcinosis, additional anti-inflammatory approaches may also be indicated: first, when calcinosis is depositing or increasing in size, it is our experience that the underlying JDM is usually active. In addition, the calcinosis lesions often have an intense chronic inflammatory infiltrate surrounding them, as discussed above. Thus, anti-inflammatory approaches may be expected to aid in preventing further deposition, but not necessarily in resolving existing lesions.

Marked regression of calcinosis, as well as retardation or progression following treatment for 2 – 10 months with hydroxychloroquine, intravenous immunoglobulin, cyclosporin, and most recently with infliximab has been observed in a limited number of reported cases (Table 2). Intra-lesional triamcinolone acetate administered monthly for up to 12 months has resulted in improvement in the size of lesions in several patients (39,40). Colchicine (0.5 mg qd – tid) has been effective for the both localized and systemic (febrile) inflammation associated with calcinosis, as well as in healing ulcerations, but it has no reported effect on the size of the lesions (41,42).

There is no published data on the effectiveness of other agents, including oral corticosteroids, methotrexate, or azathioprine in treating calcinosis, and a few anecdotal cases of worsening while patients have received these agents (43). Overall, the effectiveness of a particular agent appears to depend on its success in controlling the underlying inflammatory process, and many agents are potentially partially beneficial.

Other therapeutic approaches have aimed to inhibit deposition of calcinosis through other mechanisms particularly aimed at disrupting calcium-phosphorous homeostasis. The most studied agent of these is diltiazem, a calcium channel-blocking agent. It is hypothesized that this agent may inhibit calcium influx into cells and decrease intracellular muscle calcium concentration (44). Most reports using diltiazem in the treatment of calcinosis have been positive: nine patients with JDM or systemic sclerosis (SSc) have experienced a reduction in lesion size after receiving a high dose of 240 – 480 mg per day (4 – 6 mg/kg/d) over a relatively long duration of time of 1 – 12 years (44-49). Some patients have also experienced total resolution of their calcinosis and no new calcifications forming. One report, however, demonstrated radiographic improvement in calcinosis in only 3 of 12 SSc patients, calling into doubt the efficacy of diltiazem therapy for calcinosis; however, the doses used in this study were lower at 180 mg daily (50). Potential side effects of diltiazem therapy include anecdotal reports of myositis exacerbation (Rider and Miller, unpublished), hypotension, dizziness, headache and nausea/vomiting.

A second class of agents has aimed to decrease the intestinal absorption of phosphate, using aluminum hydroxide therapy, or to increase the renal excretion of phosphate, using probenecid therapy. Both agents would potentially result in a reduction in the calcium-phosphorous product in plasma and may decrease calcium deposition in tissues. Eleven patients with JDM or SSc treated with relatively high doses of these agents for 2 – 18 months experienced a reduction in the size of calcinosis deposits or resolution of the lesions (8;51-59). A case of dechallenge - rechallenge with probenecid therapy (deterioration when treatment was interrupted and marked improvement in lesion size when it was restarted) provides additional support of benefit in one patient (59). Notable side effects of these agents include

gastrointestinal for aluminum hydroxide and a decrease in the renal tubular secretion of methotrexate and non-steroidal anti-inflammatory drugs with probenecid.

Therapy with bisphosphonates is another potentially promising approach. These agents are being used as therapy for disorders resulting in hypercalcemia, osteoporosis, and some calcification processes, including myositis ossificans and arterial calcifications (60). Proposed mechanisms of bisphosphonates in these disorders, including dystrophic calcification, include inhibition of calcium hydroxyapatite formation, macrophage function and bone calcium resorption (61-63). Of note, bisacylphosphonates such as pamidronate, due to structures with shorter carbon chains and keto side groups, have enhanced functions in these mechanisms much more than etidronate, which has previously not been beneficial for calcinosis in JDM (62,64,65). Two JDM patients have experienced a dramatic improvement and near resolution of extensive calcinosis 2 – 12 months after initiation of these agents (22,47). One patient also received diltiazem in combination. Of note, the doses utilized have been higher than are typically used to treat osteoporosis: 10 mg daily for alendronate and 4 mg/kg/day orally for pamidronate.

Several additional agents have been tried in therapy for calcinosis, but currently appear to be less promising approaches. Anecdotal improvement with warfarin, which inhibits carboxylation of matrix Gla-containing proteins, was apparent in early reports (66). A double blind, placebo-controlled trial, however, suggests no benefit, and there is also a potential for hemorrhagic complications (67,68). Magnesium sulfate has been tried in other calcification conditions, but has apparently mixed benefit in JDM patients (69,70). High-energy repetitive ultrasound therapy has been associated with pain reduction in patients with calcific tendonitis; however, there is potential for flare of local inflammation (71).

For certain patients, physical medicine approaches are helpful adjuncts, including cushioning and extending range of motion with the use of heat and gentle serial casting. Patients should be advised to avoid traumas and minor tissue injuries. For some patients with tumorous deposits, surgical removal is indicated, including for patients experiencing chronic or severe pain, loss of function, recurrent infections or drainage, or a non-healing ulcer (18,72-74). Potential complications of surgery include problems with wound healing and recurrence (18). This tends to be uncommon with good control of the myositis prior to undertaking surgery, use of low doses of corticosteroids to minimize disruption to wound healing, as well as with minimization of surgical irritation and trauma (18).

In summary, dystrophic calcification as a sequelae of JDM is associated with prolonged or inadequately treated JDM disease activity, and has the potential to possibly be prevented through early, aggressive immunosuppressive therapy for JDM. Depositing calcinosis is also frequently associated with not only active JDM, but a pro-inflammatory process surrounding the lesions. Early intervention with immunosuppressive agents may be helpful in prevention of

further deposition. The development of better outcome measures and studies involving randomized controlled trials are needed to develop evidence-based therapies for this complication. A better understanding of the pathogenesis of calcinosis should aid in improving its treatment.

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Figure 1. Subtypes of dystrophic calcification in juvenile Dermatomyositis (JDM).

- A. Superficial plaques or nodules are confined to the skin or subcutaneous tissue and have been reported in 33% of JDM patients with calcinosis in one series (5,9).
- B. Tumoral deposits, also known as calcinosis universalis, are larger nodular deposits that may extend to deeper tissue layers, including the muscles. They have been reported in 20% of patients developing calcinosis (5,9).
- C. Fascial planar deposits occur along the fascial planes of muscles and tendons, manifest in this radiograph as linear deposits. Fascial plane deposits have been observed in 16% of patients in one series (5,9).
- D. Exoskeleton is an extensive, hard calcium deposit over the entire body surface area, manifest here as widespread calcinosis on this chest radiograph from a girl with JDM. This has been seen in 10% of JDM patients developing calcinosis (5,9). Twenty-two percent of JDM patients with calcinosis have a mixture of subtypes.

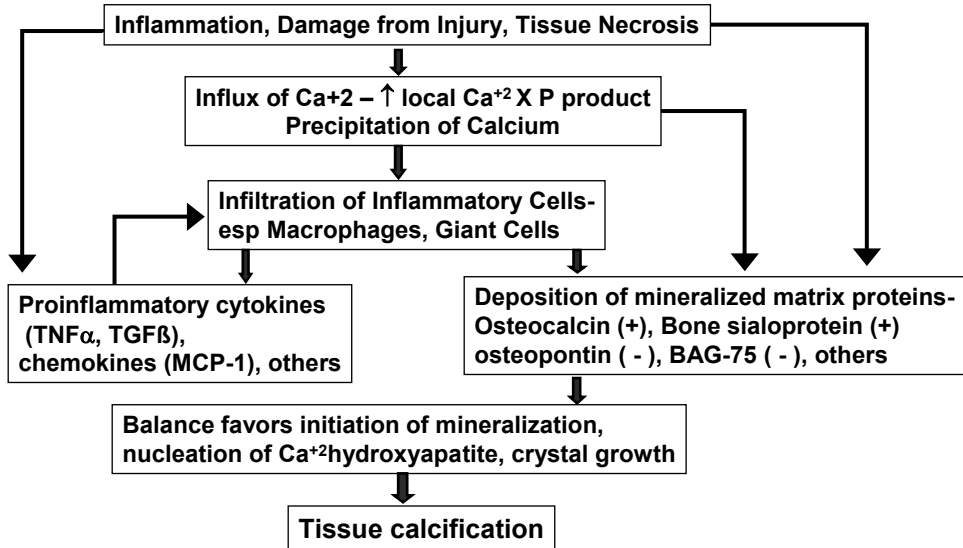
**Table 1.** Possible risk factors for development of calcinosis in juvenile dermatomyositis.

<b>Associated with development of calcinosis</b>	<b>References</b>
Delay in diagnosis or treatment	(3,10)
Inadequate or delayed corticosteroid treatment	(5)
Longer duration active disease	(3)
Chronic or polycyclic disease course	(11)
Low anti-nuclear antibody titers, but PM-Scl autoantibody	(11,12)
Higher initial level of creatine kinase, longer duration elevated serum levels of muscle enzymes	(3,13)
TNF- $\alpha$ -308A promoter region polymorphism	(23)
Minor tissue injury, trauma	Anecdotal

Figure 2. Hypothesis of the Pathogenesis of Calcinosis in Juvenile Dermatomyositis.

+ = initiates or promotes mineralization; - = inhibits mineralization

## Hypothesis of Pathogenesis of Calcinosis



**Table 2.** Immunosuppressive or anti-inflammatory therapies for calcinosis in juvenile dermatomyositis.

<b>Immunosuppressive/Anti Inflammatory Agents</b>	<b>Dose</b>	<b>Effects, Comments</b>	<b>References</b>
Hydroxychloroquine	2 -5 mg/kg/day	Improvement in elbow calcification after 6 months in 1 patient	(75)
Intravenous immunoglobulin (IVIG)	2 gm/kg/month	Marked regression of calcinosis after 3 -6 months in 3 patients	(76-78)
Cyclosporin	5-6 mg/kg/day	Partial to complete resolution of calcinosis after 3-6 months in 3 patients	(79)
Infliximab	3-5 mg/kg/dose	Retarded progression; partial to marked regression of calcinosis, decreased associated pain after 2-10 months therapy in 2 patients	(80)
Colchicine	0.5 mg qd-tid	Effective for local and systemic inflammatory signs associated with calcinosis. No effect on size of lesion.	(41,42)
Triamcinolone acetonide injection	≤ mg q 1-2 months, total 10-12 injection	Regression of deposits at local site of intralesional injection	(39-40)

**Table 3.** Additional anecdotal therapeutic approaches for the treatment of calcinosis in juvenile dermatomyositis (JDM).

Agent	Dose/Duration	Proposed Mechanism	Effects, Comments	References
Diltiazem	240-480 mg qd (4-6 mg/kg/d) ÷ tid - qid/1-12 years duration	Prevent further deposition of calcinosis by inhibiting calcium influx into cells, decreasing intracellular and intramuscular calcium concentrations	Reports of benefit in 9 patients with JDM, systemic sclerosis: reduction in size of lesions to total resolution; no new lesions. One negative report: only 3 of 12 systemic sclerosis patients developed radiographic improvement.	(44)
Aluminum Hydroxide	15 ml tid-20 ml qid (1.7-3.6 gm aluminum qd, ~30-75 mg/kg/d)/ 6-18 months duration	Produces aluminum phosphate --> decreases intestinal absorption of phosphate --> reduces CaP product in plasma --> inhibits crystallization of calcium in tissues (54,55)	Reduction to resolution of calcium deposits in 5 patients with JDM	(8,51-53)
Probenecid	250 mg qd-500 mg qid (~8-30 mg/kg/d)/2-18 months duration	Increases renal tubular phosphate reabsorption --> decreases serum phosphorous --> reduces CaP product in plasma --> reduces tissue deposition of calcium (54,55)	Reports of benefit in 7 patients with JDM, systemic sclerosis, Still's disease: reduction in size of calcinosis deposits, no new lesions. One report of deterioration when therapy resolution of widespread lesions. One also treated simultaneously with diltiazem.	(54-59)

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