REVIEW

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Calcinosis in dermatomyositis

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Purpose of review
To provide the most recent literature on our understanding behind the pathogenesis and the treatment of calcinosis in dermatomyositis.

Recent findings
Early diagnosis and controlling the overall disease activity are cornerstones to prevent calcinosis in juvenile dermatomyositis. Observational cohort studies showed that prolonged state of inflammation and features of vascular dysfunction like digital ulcers and abnormal nailfold capillaries are associated with calcinosis. Neutrophil activation and mitochondrial dysfunction have recently emerged as potential mechanistic pathways involved in calcinosis pathogenesis. Few recent case series have alluded to the efficacy of topical and intralesional sodium thiosulfate, while JAK inhibitors appear to be newer promising therapy in juvenile dermatomyositis.

Summary
Calcinosis in dermatomyositis consists of deposition of insoluble calcium compounds in the skin and other tissues. It is prevalent in up to 75% of patients with juvenile dermatomyositis and up to 20% in adult dermatomyositis. While it leads to significant patient morbidity, we do not yet understand the pathogenesis in its entirety. Surgical excision although palliative is the mainstay of treatment and should be offered to patients. All available treatment options are only based on very low level of evidence.

Keywords
calcinosis, dermatomyositis, JAK inhibitors, mitochondria, neutrophil, sodium thiosulfate, therapeutics

INTRODUCTION

Dermatomyositis is an autoimmune connective tissue disease with a wide phenotypic heterogeneity. While its hallmark features include distinctive skin manifestations and myopathy, it also exhibits other manifestations like inflammatory arthritis, calcinosis, interstitial lung disease, malignancy and occasional gastrointestinal involvement, often correlated with specific autoantibodies [1–6]. In dermatomyositis, calcinosis is dystrophic, with insoluble calcium compounds (hydroxyapatite or carbonate apatite) deposited in the skin and other tissues, in the setting of normal serum calcium and phosphorus levels [7]. Its prevalence in juvenile dermatomyositis (JDM) ranges from 20 to 75%, depending on the racial demographics and composition of the study population and up to 20% in adult dermatomyositis [1,4,8–14].

Clinically, calcinosis in dermatomyositis can present as superficial or deep dermal nodules (sponge-like appearance on plain radiographs), tumoral form (mass-like appearance on plain radiographs) and extensive sheet-like where it is termed as calcinosis universalis [15]. A more recent study employing whole-body computed tomography (CT) identified five distinct patterns of calcinosis in dermatomyositis: clustered, disjoint, interfascial, confluent and fluid-filled [16]. Extremities, trunk and especially pressure points are commonly affected areas. Calcinotic lesions often cause significant amount of pain, reduced range of motion when near joints, ulceration and secondary infections, all contributing to the morbidity in dermatomyositis. A recent analysis of patient-reported surveys showed a significant physical and psychosocial burden from dermatomyositis in almost 50% of the respondents also leading to unemployment [17]. Moreover, a

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KEY POINTS

- Early diagnosis and controlling the overall disease activity are cornerstones to prevent calcinosis in juvenile dermatomyositis.
- Neutrophil activation and mitochondrial dysfunction have emerged as potential mechanistic pathways involved in calcinosis pathogenesis.
- Surgical excision although palliative is the mainstay of treatment and should be offered to patients.
- Recent case series have alluded to the efficacy of topical and intralesional sodium thiosulfate in treatment of calcinosis.

cost-analysis study determined that dermatomyositis patients incurred a five-fold higher total annual costs compared to matched controls [18].

CLINICAL ASSOCIATIONS

Although calcinosis is much more frequent in JDM compared to adult dermatomyositis patients [10], it is frequently associated with prolonged state of persistent disease and/or severe disease activity in both [12,19]. Delay in diagnosis further adds to this risk especially in JDM patients [12,20]. While the presence of digital ulcers is associated with the presence of calcinosis in adult dermatomyositis [21], nailfold capillary abnormalities at baseline were predictive of development of calcinosis in JDM patients [22].

The role of race and ethnicity in development of calcinosis has been studied in several recent investigations, with inconsistent results ranging from lower to higher prevalence of calcinosis in individuals from racial and ethnic minorities as compared to White patients [23–25]. However, none of the studies have adjusted for disease severity which could be a potential confounding factor.

The presence of MDA-5 (melanoma differentiation associated protein 5) antibody and/or NXP-2 (nuclear matrix protein-2) antibody is highly associated with calcinosis in dermatomyositis amongst most racial groups [1,2,4,6,26,27]. Moreover, the presence of calcinosis is associated with poor disease outcomes in JDM patients with NXP-2 antibodies [28▪▪].

PATHOGENESIS OF CALCINOSIS

Although the exact mechanism(s) of calcinosis pathogenesis are not fully understood, the following pathways, particularly neutrophil activation [29] and mitochondrial dysfunction [30▪▪], seem to have recently emerged as novel potential processes participating in the pathogenesis of calcinosis.

Calcinosis and neutrophil activation

Despite the emergence of new advanced technologies, including spatial transcriptomics and single cell RNA sequencing, the presence and role of infiltrating neutrophils in the skin and muscle of JDM has been challenging to assess, not only due to the short life span of neutrophils but also the lack of reliable animal models of JDM calcinosis. We recently made the novel observation of neutrophils infiltrating calcified muscle tissue, engulfing mineral particles [29]. These are, to our knowledge, the first visual representations of neutrophils engaging with the local calcification, participating in its removal. However, uptake of calcium crystals promoted neutrophil-mediated inflammation and extrusion of neutrophil extracellular traps (NETs) [29].

Although we have been able to determine some of the main mechanisms contributing to neutrophil-mediated inflammation and damage in tissue, mechanisms promoting neutrophil infiltration into calcified tissue are not known. Levels of potent chemoattractant molecules, including IL-8 and complement components, have been associated with neutrophil activation in JDM [29]. Further, calcified tissue also contains mitochondrial-derived N-formyl methionine peptides [30▪▪], a potent chemoattractant signaling through formyl peptide receptor 1 (FPR1). Although we have established N-formyl methionine as an important chemoattractant molecule in several autoimmune conditions [31,32], its role in JDM pathogenesis, and in particular in calcinosis development, is still to be determined.

Neutrophil activation is also seen in peripheral blood with levels of NETs elevated in patients with calcinosis [29,33,34]. The elevated levels of NETs in peripheral blood could be due to increased frequency of low-density granulocytes spontaneously releasing NETs [34], presence of circulating immune complexes [29,33], or reduced degradation of the formed NETs [29,33], likely due to presence of NET-protective antibodies similar to what has been described in other autoimmune conditions [35]. Of note, though neutrophils are activated, both in peripheral blood and tissue, a causal link to calcinosis is not clear. The data indicate a response to calcinosis, and/or circulating danger-associated molecular patterns. However, it is also possible that neutrophil-mediated inflammation could initiate and/or amplify the pathogenesis of calcinosis. Future studies are warranted to explore the role of

neutrophils *in vivo* in the development of calcinosis and/or local tissue inflammation. Should their role in the pathogenesis be validated, several therapeutic approaches could be considered in limiting their recruitment and activation, chief of which would be reducing calcium crystal deposits in tissue as discussed below and in more detail in prior work [36▪]. There are currently no treatment specifically targeting neutrophils. Several companies are developing inhibitors of NET formation, primarily focusing on PAD. However, given NET formation in JDM seem to be PAD-independent [29], other avenues will have to be considered. Potential targets would be NADPH oxidase inhibitors, enzymes involved in NET formation (such as neutrophil elastase), and/or targeting NET degradation itself by DNases [37]. Finally, main chemotactic signals, for example, IL-8, N-formyl methionine, and C5a, are all present in JDM, and should be explored for their role in recruiting inflammatory myeloid cells into tissue [29,38,39].

Calcinosis and mitochondria

Mitochondria play an essential role in calcium homeostasis within the cell, linking scavenging of calcium through the mitochondrial calcium uniporter (MCU) with uptake of phosphate for the assembly of amorphous hydroxyapatite [40]. In assessing muscle biopsies from JDM patients with calcinosis, we made the novel finding of profound intramitochondrial calcification in skeletal muscle cells [30▪▪]. In recapitulating these findings in vitro, mitochondrial calcification was amplified by type I interferons, commonly seen in patients with JDM [30▪▪]. Mechanistically, type I interferons caused mitochondrial stress, oxidizing MCU resulting in unregulated uptake of calcium and phosphate to the mitochondria, subsequently precipitating as hydroxyapatite [30▪▪]. The calcified mitochondria failed to perform oxidative phosphorylation, and released its nucleic acids into the cytosolic compartment, triggering interferon production through the cGAS/STING pathway establishing a vicious cycle of inflammation-mediated mitochondrial calcification and cell death.

Mitochondria were not only retained within the skeletal muscle cell, but also released into tissue, likely as a result of cell death. These observations translated to elevated levels of extracellular mitochondria, including mitochondrial DNA, in peripheral blood of patients with JDM, primarily associated with calcinosis. Of note, mitochondria, due to their prokaryotic origin, are immunogenic. Other than inflammation, such as mediated by oxidized mitochondrial DNA [41▪], extracellular mitochondria can also trigger development of antimitochondrial antibodies. Antimitochondrial antibodies are frequently seen in rheumatic diseases, including anticardiolipin antibodies, targeting mitochondrial-derived phospholipids [42]. Using an in-house flow cytometry assay, measuring antibodies targeting outer mitochondrial membrane antigens, 40% of patients with JDM had antimitochondrial antibodies. Further, presence of antimitochondrial antibodies was enriched in patients with calcinosis (close to 70%). In patients without diagnosis of calcinosis, presence of antimitochondrial antibodies predicted development of future calcinosis [30▪▪]. If validated, these findings indicate that mitochondrial dysfunction, extrusion and formation of antimitochondrial antibodies are early events in the calcinosis pathogenesis. This could provide for an important therapeutic window prior to clinical development of calcinosis where interventions could have substantial effect in limiting, or even preventing, calcinosis. *In vitro*, targeting mitochondrial ROS completely blunted mitochondrial calcification and subsequent inflammation. Prior work in animal models of other rheumatic diseases, including lupus [43] suggest scavenging mitochondrial ROS may be a potential target to consider in JDM, in particular in preventing excessive mitochondrial damage and calcification. Other therapeutic options will be discussed in more detail below, including JAKi that potently may interfere with inflammation/interferon-mediated amplification of the calcinosis pathway.

Vascular dysfunction

A single-center retrospective study on JDM patients ($N = 172$) found that the presence of nailfold capillary abnormalities at baseline was highly predictive of future calcinosis, when adjusted for age, biological sex, and disease duration (hazard ratio = 4.98) [28▪▪]. Apolipoprotein A-1 (apoA-1), a component of HDL molecule, is a major inhibitor of vessel wall inflammation. A cross-sectional study of 27 dermatomyositis patients, showed significantly lower circulating apoA-1 levels in the calcinosis group, when adjusted for age, disease duration, and severity [odds ratio (OR) = 11.49] [44]. These studies indicate a potential role for vascular dysfunction in calcinosis development in dermatomyositis.

Genetic associations

Whole genome sequencing of systemic sclerosis (SSc) and dermatomyositis patients ($N = 50$) with a severe calcinosis phenotype showed the presence of rare singleton variants in *ABCC6* and *ENPP1* genes. These genes regulate generation of inorganic

pyrophosphate, an inhibitor of mineralization [36▪]. The role of the identified gene variants in regulation of inorganic pyrophosphate is currently unknown.

IMAGING MODALITIES

Plain radiographs have been an age-old modality to detect calcifications, but their two-dimensional perspective often falls short of accurate assessment. Low-dose whole-body CT seems promising in capturing the physical burden of calcinosis [16]. While its cost-effectiveness must be studied further, ultrasound has emerged as an easy point-of-care diagnostic modality in rheumatology clinics [45] and its ability to detect calcinosis is currently being studied in SSc.

Employing durometry to identify calcinosis by measuring its firmness also fared well in a recent study, especially in sites such as upper neck/clavicle as well as upper and lower extremities [46].

THERAPEUTICS

Calcinosis in dermatomyositis continues to be an unmet need, not only because of its unclear pathogenesis, but also due to the lack of large clinical trials and validated outcome measures. Most of the treatments that are currently employed are based on low research evidence. While a comprehensive list of pharmacological therapies has been outlined in a recent review article [36▪], we have only included the latest published data on pharmacological and nonpharmacological approaches herein.

Nonpharmacological approach

Surgical excision

Despite being a palliative option, surgical excision seems to be the most effective way to treat bulky calcinotic lesions or calcinosis presenting around joints restricting range of motion [47].

Minimally invasive procedures

Few case series reported improvement of dystrophic calcinosis when treated with intralesional sodium thiosulfate (STS) given as monthly injections of 1–1.2 ml of 250 mg/ml STS solution per lesion [48–50]. However, a small double-blind controlled study ($N = 4$) where each participant contributed one lesion each to the treatment and control group, only one lesion responded in the treatment group, and overall, there was no difference between the treatment and control groups at the end of 3 months [49].

Shiari *et al.* [51] conducted an open label clinical trial of intralesional infliximab with local anesthesia to five patients with JDM and calcinotic lesions less than 5 cm^2, given every week over a period of 16 weeks. Dosing at 20 mg infliximab for lesions 1.5 cm^2 or less and 40 mg for lesions 1.5–5 cm^2 showed significant reduction in the size of the lesions [51].

Microneedling with inkless tattoo showed nearly 80% reduction of calcinotic nodules in one dermatomyositis patient, probably by stimulating the intrinsic wound healing cascade [52▪].

Further studies are needed to validate these initial, and yet unproven, findings.

Pharmacological approach

Sodium thiosulfate

STS is a calcium chelating agent and may increase the solubility of calcium salts. A study on topical STS (25% STS compounded) in patients with ectopic calcifications ($N = 28$), including 14 dermatomyositis patients (six adults, eight children), showed higher number of responders (radiographically determined) in children compared to adults (54.5 vs. 17.6%). While most patients did not experience any pain or adverse effects related to the local application, one dermatomyositis patient reported transient increase in local inflammation and pain, which later resolved spontaneously, allowing the patient to resume STS treatment [53▪▪]. A case report of a 44-year-old patient with calcinosis in dermatomyositis, showed an analgesic response to topical 20% STS compounded 1 : 1 with vaseline, when applied daily for 1 month [54].

A single-center retrospective study of seven patients with dystrophic calcinosis who received either intravenous (i.v.) or oral STS, administered over a mean of 4.5 months for i.v. and 29.1 months for oral formulations, respectively, showed a partial response in four patients. Pain, ulceration and inflammation associated with calcinosis improved with this treatment.

Bisphosphonates

Bisphosphonates can reduce bone turnover and impede macrophage activity leading to reduced inflammation. Bisphosphonates are frequently used in JDM-associated calcinosis. A retrospective study on 42 JDM patients with calcinosis showed that drugs affecting calcium/phosphorus metabolism, including bone metabolism, were significantly associated with improvement of calcinosis [26]. A previous case series reported improvement of calcinosis

in four of six JDM patients treated with i.v. pamidronate or oral alendronate 70 mg per week over a period of 3 months [55]. Also, a more recent case report on JDM-associated calcinosis showed significant reduction in the calcinotic burden radiographically when treated with IV pamidronate for 2 years [56].

JAKi (Janus kinase inhibitors)

The JAK-STAT signal transduction system mediates inflammation via several inflammatory mediators, including type I interferons. A retrospective study on 88 JDM patients treated with at least 3 months of tofacitinib showed reduction in calcinotic burden in 12 of 17 patients with calcinosis [57]. Another retrospective study of 75 JDM patients showed that tofacitinib relieved calcinosis in three of six patients who had refractory JDM and calcinosis [58].

While a case series of three patients with adult dermatomyositis (2 had anti-NXP2 positivity) showed radiographic improvement within 3 months [59], an independent case report showed significant regression of calcinosis along with lowering the interferon score in an anti-NXP2 positive dermatomyositis patient when treated for 9 months with tofacitinib [60].

Another JAKi, baricitinib, also halted the progression of calcinosis in a recalcitrant anti-NXP-2 positive JDM patient with severe calcinosis [61].

Tumor necrosis factor inhibitors

High levels of TNF-α (tumor necrosis factor-α), released by activated macrophages and T cells, are seen in patients with active JDM and calcinosis. A retrospective study in JDM patients, receiving either infliximab or adalimumab for at least 3 months, showed improvement in 54% of those with calcinosis ($N = 28$) over a median treatment duration of 2.7 years [62].

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) has been shown to reduce disease activity in dermatomyositis by reducing the deposition of membrane attack complex in the affected tissues as well as decreasing T-cell activation. Among the various immunomodulatory and calcium-modifying therapies, IVIG seemed to show the greatest benefit (hazard ratio 1.95) for calcinosis based on a recent retrospective study of the CARRA registry (Childhood Arthritis and Rheumatology Research Alliance) ($N = 63$) [63]. A few case reports have shown that IVIG improves calcinosis at doses of 2 g/kg/month after five to six courses in both juvenile as well as adult dermatomyositis [64,65].

CONCLUSION

Calcinosis contributes to significant morbidity in dermatomyositis patients yet remains a greatly unmet need in terms of available treatments. Neutrophil activation, mitochondrial dysfunction, and vascular dysregulation seem to play a role in the development of calcinosis. Prompt diagnosis and controlling the overall disease activity can help prevent calcinosis in JDM. While bisphosphonates have been an age-old treatment for calcinosis in JDM, JAKi are emerging as a promising avenue for anti-NXP-2 positive dermatomyositis patients with high interferon scores. Microneedling and intralesional STS treatment of calcinotic nodules are novel approaches, but need larger studies to validate their effectiveness. Surgical resection still provides the most effective and immediate relief and should be considered for accessible lesions.

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Conflicts of interest

There are no conflicts of interest.

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