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Treatment of calcinosis cutis in systemic sclerosis and dermatomyositis: a review of the literature

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Abstract:

Background: We have limited data on the treatment of calcinosis cutis associated with systemic sclerosis (SSc) and dermatomyositis (DM).

Objective: To assess the efficacy and tolerance of available treatments for calcinosis cutis based on previously published studies.

Method: We performed a systematic review of studies published in MEDLINE, Embase, and the Cochrane library between 1980 and July 2018. The strength of clinical data was graded according to the modified Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Results: In all, 30 studies (288 patients) were included. Eleven therapeutic classes, surgery and physical treatments were identified as potential treatments for calcinosis cutis. From the results of a small randomized controlled trial and 4 retrospective studies, low-dose warfarin should not be used for calcinosis cutis (Level IB evidence). Several studies suggested the use of diltiazem and bisphosphonates (Level IV). Considering biologic therapies, rituximab has shown interesting results in both DM and SSc, whereas TNF inhibitors may be useful in juvenile DM (Level IV). Intralesional sodium thiosulfate may be a promising alternative (Level IV).

Limitations: Few included studies had a high level of evidence.

Conclusion: This study highlights the efficacy and tolerance profiles of available treatments for calcinosis cutis, with a focus on level of evidence.

Key words: calcinosis cutis, systemic sclerosis, dermatomyositis, level of evidence

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INTRODUCTION

Calcinosis cutis is defined by the deposition of insoluble calcium in the skin and subcutaneous tissues.[1] DM and SSc are the most frequent autoimmune connective tissue disorders associated with calcinosis cutis.[2] Indeed, calcinosis cutis develops in about 30% of adult DM patients[3] and 30% to 70% of juvenile DM patients.[4–7] Moreover, the prevalence of calcinosis ranges from 18% to 49% in SSc patients.[8–12] Significant advances in understanding the SSc and DM pathogenesis, newer classification criteria and advances in disease management have resulted in improved survival in SSc and DM.[4,5,13] Nevertheless, long-term morbidity remains a major issue.[14,15]

Dystrophic calcinosis is associated with considerably impaired quality of life due to ulceration and secondary infections, both resulting in extreme debilitation.[7,16] Although early aggressive intervention may prevent calcinosis cutis development,[17–19] treatment remains challenging. Furthermore, few randomized controlled trials (RCTs) have been performed[20] and we lack specific guidelines for calcinosis cutis management in DM or SSc. However, several case series or prospective cohort studies focusing on calcinosis cutis treatment have been published.[21]

To better define an evidence-based treatment approach and to provide the best available evidence for physicians, we performed a systematic review of case series and cohort studies investigating the management of calcinosis cutis in patients with DM or SSc.

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MATERIAL AND METHODS

This systematic review was performed according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[22]

Literature search and information sources:

We performed a systematic review of MEDLINE/PubMed, Embase and the Cochrane database between January 1980 to July 2018, with no restriction on language. The search strategy combined free text search, exploded MESH/EMTREE terms and all synonyms of the following Medical Subject Headings terms: systemic sclerosis, dermatomyositis, calcinosis cutis**.** The grey literature was also explored to avoid publication bias. We also searched for additional articles from the reference lists of relevant papers.

Study selection and eligibility criteria

Observational studies or RCTs were considered if 1) they included patients with DM or SSc; 2) the number of patients with calcinosis cutis was available; 3) patients received a specific treatment for calcinosis cutis or for the connective tissue disease with a specific assessment of calcinosis cutis outcomes; and 4) the number of patients treated and the number of responders were available. Given the rarity of calcinosis cutis but to avoid publication bias based on single case reports, we excluded case series of fewer than 3 patients along with reviews, editorials and guidelines (**Figure 1**). The quality of studies was assessed by the Newcastle-Ottawa Assessment Scale[23] for observational studies and the Cochrane collaboration Risk of Bias tool [24] for RCTs.

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Data extraction and assessment of calcinosis cutis outcomes

The post-treatment calcinosis cutis response was reported as complete or partial. Complete response was defined as the complete disappearance of calcinosis cutis, and partial response was any improvement according to the study protocol, which included reduction in the size of calcinotic deposits and healing of ulcerations. When only pain reduction was reported, the treatment was considered a failure. Adverse events were recorded. The relapse rate was defined as the reappearance of lesions after a complete or partial response. All data were extracted independently by 2 investigators. In the tables, when data were available, adult and pediatric patients are presented separately.

Levels of evidence and treatment recommendation:

The strength of clinical data and subsequent treatment recommendations were graded according to the modified Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation.[25]

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RESULTS

Literature search and characteristics of included studies

Our literature search identified 3032 citations; reports for 30 studies [10,20,26–53] were included in this systematic review **(Figure 1)**, including 2 RCTs,[20,30] 11 prospective cohort studies[31,32,36,43–48,51,53] and 17 retrospective studies.[10,26–29,33–35,37–42,49,50,52] The sample size ranged from 3 to 78 patients, for a total of 288 patients (SSc=108, adult DM=66, juvenile DM=90, and DM or SSc but unspecified diagnosis=24).

Overall, the methodological quality of included studies was low, with 26 cohort studies graded as poor quality and only 2 as fair quality.

Warfarin: Warfarin, a vitamin-K antagonist, was used in one RCT[20] and 4 retrospective studies[26–29], with a total of 19 patients (DM=10, SSc=6, unspecified=3) **(Table 1)**. A dosage of 1 mg/day was most commonly prescribed. The mean calcinosis cutis duration was from 4 months[27] to 10 years.[26] A small placebo-controlled trial[26] found no clinical improvement in calcinosis cutis in 5 patients who received warfarin 1 mg/day. From the results of 5 studies, the partial response rate ranged from 0% [20,26,29] to 2/3 (66%) [28,54], with no complete response observed in all but one study (2/3; 66%).[54] No relapse was observed after 2 years' follow-up in one study.[27] Adverse events were not reported.

Diltiazem: Diltiazem, a calcium channel blocker, was used in 3 retrospective cohort studies in 38 patients (DM=12, SSc=12, unspecified =14)[10,28,29] **(Table 1)**. The dosage ranged from 60 mg 3 times daily to 480 mg/day. The partial response rate ranged from 0/12 (0%)[29] to 9/14 (64%).[28] No complete responses were reported in the 3 studies and no adverse events were reported in the study of Vayssairat et al.[10]

Rituximab: Rituximab was used in 7 studies (SSc=18, adult DM=9, juvenile DM=32) including 3 prospective studies,[31–33] 3 retrospective studies[29,34,35] and one RCT versus placebo

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focusing on the efficacy of rituximab on skin lesions including calcinosis cutis.[30] Study characteristics are summarized in **Table 2**. The mean calcinosis cutis duration ranged from 3.4 to 12 years.[33,34] From the results of 6 studies, the partial response rate ranged from 0/6 (0%) [34] to 100% in 3 studies including 3 to 9 patients.[31,32,35] The complete response rate ranged from 0%[29,33,34] to 100% in a study of 3 SSc patients.[31] In 2 studies, the relapse rate was 0% with a follow-up of 12 to 60 months.[31,35] Adverse events were assessed in 3 studies and included localized bacterial infection of the calcinosis (n=2), moderate acute infusion-related events (n=1), and intestinal perforation 2 weeks after a combination of rituximab and pulse methylprednisolone infusions (n=1).

Other biologic agents: Tumor necrosis factor α (TNF-α) inhibitors and abatacept (CTLA4-Ig) were used in 4 studies[29,36–38], with a total of 30 DM patients (mostly juvenile DM). The results of 3 infliximab studies[29,36,38] showed a partial response rate ranging from 0% (0/2)[29] to 80% in a prospective study of 5 juvenile DM patients[36]. No complete responses were noted and adverse events were not reported.

Bisphosphonates: Four retrospective cohort studies of 17 individuals (DM=15, unspecified =2)[28,39–41] assessed the efficacy of bisphosphonates for calcinosis cutis (**Table 3**). Specific bisphosphonates and the therapeutic regimens were heterogeneous. The partial response ranged from 3/6 (50%)[40] to 3/3 (100%)[39] and the complete response rate from 0% to 33%.[28,39–41]. In 2 patients receiving pamidronate with complete response, one relapse was noted after 4 years; in this case, alendronate was then used, which resulted in a second complete response. No adverse events were recorded in the only study assessing safety.[41]

Intravenous immunoglobulins: Two retrospective studies including 15 DM patients[29,42] assessed the efficacy of intravenous immunoglobulins on calcinosis cutis. Galimberti et al.[42] reported a partial response in 5/8 (62%), with no complete responders. Conversely, no

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objective response was observed in the study of Fredi et al.[29] including 7 DM patients, with only one reporting pain improvement. Adverse events were not reported in these studies.

Sodium thiosulfate (STS): Five studies[29,48–51] assessing different regiments of STS or its metabolites involved 20 patients (SSc=9, adult DM=10, juvenile DM=1). Two studies[48,49] of 7 patients assessed the efficacy of intravenous STS. No objective improvement was found, and pain improvement was noted in only one patient.[49] Topical STS conferred no improvement in 5 DM patients.[29] Partial response was achieved with topical sodium metabisulfite (a metabolite of STS) in 3/3 patients (2 DM and 1 SSc), without relapse,[50] including one with complete response. Finally, in a prospective study, partial response was achieved in 5/5 SSc patients, including complete response in 2 receiving intralesional STS injection.[51] Adverse events of intralesional STS included transient pain (n=2/5) and local infection (n=1/5).[51]

Minocycline: Minocycline (50-200 mg/day) was used in 2 studies of 12 patients (SSc=9, unspecified=3).[28,52] Robertson et al. [52] reported a partial response in 8/9 patients and Balin et al.[28] a partial response in 1/3. Adverse events included nausea (n=1), dizziness (n=1) and the conversion of calcinosis cutis deposits to a blue/black color.[52]

Colchicine: Balin et al.[28] found a partial response in 3/7 patients (43%), including 1/7 with complete response using colchicine doses < 1.2 mg/day. Fredi et al.[29] reported only 1/9 partial response with colchicine.

Cyclophosphamide: One prospective study used cyclophosphamide for treating refractory or severe juvenile DM, including 14 patients with calcinosis cutis.[53] Complete response of calcinosis cutis was noted in 9/14 (64%), with a follow-up between 12 and 24 months.

Surgery and physical therapies: Five prospective studies and one retrospective study (n=55 patients: SSc=26, DM=1, unspecified=28) assessed surgical intervention and physical therapy

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for calcinosis cutis improvement[28,43–47] (**Table 3**). Surgical excision in 2 studies led to 80% improvement.[47] Balin et al.[28] reported a partial response of 27/28 (96%), including 22/28 (79%) with complete response. Two small prospective cohort studies of 7 patients noted a partial response rate of 33% to 100% with extracorporeal shock-wave therapy, with no complete response.[44,45] The relapse rate was not reported. Adverse events included transient pain with extrusion of calcific debris. Another prospective study of 6 SSc patients reported a partial improvement rate of 83% with a carbon dioxide laser.[43] Adverse events included poor wound healing (n=5), hyperkeratosis (n=4) and postoperative infections (n=2). Relapse was observed in 2/6 patients within 3 to 4 months.[43]

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DISCUSSION

In this systematic review, we identified 30 studies (288 patients) focusing on the treatment of calcinosis cutis associated with SSc and DM. **Table 4** summarizes the available treatments for calcinosis cutis with a focus on underlying diseases and levels of evidence.

Currently, we lack specific guidelines for managing calcinosis cutis in autoimmune connective tissue disorders. In the recent consensus-based recommendations for the management juvenile DM, an intensification of immunosuppressive therapy was suggested, but no specific treatment was recommended.[19] Moreover, treatment of calcinosis cutis is not included in the updated EULAR recommendations for treating SSc.[55]

From our systematic review, several drugs used to treat calcinosis cutis have potential therapeutic interest. Because of the small number of patients and the treatment heterogeneity among included studies, pooled response rates were not calculated. However, several important findings may be underlined. From the results of a small RCT, warfarin conferred no improvement in calcinosis cutis[56], and no partial response was observed in most included studies.[20,26,29] Therefore, warfarin should not be considered for treating calcinosis cutis. This suggestion is further supported by the fact that warfarin could promote ectopic calcification via under-carboxylated matrix gla protein.[57]

Despite no complete response noted in the 3 studies of diltiazem, partial response was observed in some, particularly in Balin et al., in 9/14 (64%) patients. Some data support the use of calcium channel blockers for calcinosis cutis in SSc. Indeed, digital ischemia was strongly related to the occurrence of calcinosis cutis in a large study of 1300 SSc patients, and the use of calcium channel blockers was inversely associated with the presence of calcinosis cutis in this study.[12] Moreover, the use of calcium channel blockers is recommended for treating Raynaud phenomenon in SSc.[55] Therefore, although no formal

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curative effect of diltiazem on calcinosis cutis could be demonstrated, a potential preventive effect cannot be ruled out, and therefore diltiazem may be considered for treating digital calcinosis cutis associated with SSc.

Rituximab has been increasingly used in DM and SSc because of favorable outcomes in DM skin lesions[30] and SSc skin sclerosis and lung function.[58] From the results of 6 studies, rituximab may be considered for treating calcinosis cutis both in DM and SSc. Indeed, although one study of 6 juvenile DM patients did not reported improvement,[34] most studies showed at least partial response, including 3 with 100% partial response.[31,32,35] Moreover, 3 studies reported at least one patient with complete response.[30,31,35] TNF-α inhibitors, particularly infliximab, may have a beneficial effect on calcinosis cutis in juvenile DM, but their use should be carefully scrutinized in SSc because of reports of severe exacerbation of pulmonary fibrosis associated with their use.[59]

Bisphosphonates remain a therapeutic option mostly in DM, with at least partial response noted in 4 studies.[28,39–41] Nevertheless, a lack of substantive data precludes recommending a specific regimen of bisphosphonates.

Intravenous sodium thiosulfate seemed ineffective,[49] but intralesional treatment could be a promising alternative.[51]

Several other treatments, such as intravenous immunoglobulin,[42] minocycline,[28,52] colchicine,[28,29] and cyclophosphamide[53], improved calcinosis cutis in small case series but with limited level of evidence.

Surgery and physical therapies should be considered in calcinosis cutis, both in DM and SSc: several studies[28,47] reported response rates higher than 80%. However, the surgical management of digital calcinosis cutis in SSc may lead to skin necrosis and limited range of

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motion.[60] Less invasive procedures such as carbon dioxide laser[43] or extracorporeal shock-wave therapy[44,45] may be useful, but the level of evidence is weak.

Among the limitations of this systematic review is a possible publication bias. Given the rarity of publications related to calcinosis cutis treatment, we included case series with at least 3 patients which may have affected our results. However, single case reports were excluded, as were case series of only 2 patients, in order to reduce the bias, as previously described in systematic reviews of rare diseases.[61] Moreover, increasing the minimum number of patients to be considered for inclusion would have led to the exclusion of several treatments with high potential interest. Another limitation is the low levels of evidence of the reviewed studies. To date, only 2 small RCTs assessing improvement of calcinosis cutis have been performed,[20,30] including one with calcinosis cutis as the secondary outcome,[30] Other studies were mainly low-quality cohort studies or case series with Level IV recommendations.[25] The severity and the size and duration of calcinosis cutis disease are important confounding factors that may affect the therapeutic response. Only calcinosis cutis duration was reported in some studies, and data were inadequate to perform any subgroup analyses.

The treatment of calcinosis cutis is a major unmet need. Identifying patients at high risk of developing calcinosis cutis and its early treatment is recommended.[19] On the basis of 30 studies including 288 SSc and DM patients, this systematic review provides evidence-based guidance for practitioners.

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Abbreviation and acronym list:

Dermatomyositis: DM

Systemic sclerosis: SSc

Randomized controlled trial: RCT

Tumor necrosis factor: TNF

Sodium thiosulfate: STS

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449 **Figure Legends:**

450 **Figure 1. Flow-charts for study selection.** DM dermatomyositis, SSc: systemic sclerosis

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452 **Table 1. Characteristics of included studies evaluating the effect of warfarin and diltiazem on calcinosis cutis improvement**

Name/year	Disease (N)	Study design	Calcinosis duration at inclusion, years	Dose regimen	Partial response, N (%)	Complete response, N (%)	Follow-up, mean (range), months	Level of evidence, grade*
Warfarin								
Adults								
Berger, 1987	SSc (2)	RCT	8 (6-10)	1 mg/day	0 (0%)	0 (0%)	18	IB
Lassoued, 1988	SSc (1) DM (5)	R	10 (2-25)	1 mg/day	0 (0%)	0 (0%)	14.6 (7-28)	IV
Cukierman, 2004	SSc (3)	R	0.4	1 mg/day	2 (66%)	2 (66%)	20 (12-24)	IV
Balin, 2012	NA (3)	R	NA	NA	2(66%)	0 (0%)	104 (1-696)	IV
Fredi, 2015	DM (2)	R	NA	NA	0 (0%)	0 (0%)	201.8	IV
Children								
Berger, 1987	DM/SSc (1) DM (2)	RCT	5.3 (3-9)	1 mg/day	0 (0%)	0 (0%)	18	IB
Diltiazem								
Adults								
Vayssairat, 1998	SSc (12)	R	11.5	60mg x3/day	3 (25 %)	0 (0%)	78 (12-180)	IV
Balin, 2012	NA (14)	R	NA	≤480 mg/day	9 (64%)	0 (0%)	104	IV
Fredi, 2015	DM (12)	R	NA	NA	0 (0%)	0 (0%)	201.8	IV

453 RCT: randomized controlled trial, R: retrospective, SSc: systemic sclerosis, DM: dermatomyositis, NA: not available *according to modified Oxford Centre
454 for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation

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Table 2. Characteristics of included studies evaluating the effect of rituximab on calcinosis cutis improvement

Name/year	Disease (N)	Study design	Dose regimen	Partial response, N (%)	Complete response, N (%)	Follow-up, mean (range), months	Level of evidence, grade*
Adult							
Aggarwal, 2016[30]	DM (7)	RCT	0.575-1g/m2 at weeks 0/1	NA	1 (14%)	1.46	IB
Moazedi-fuerst, 2015[31]	SSc (3)	P	500 mg/m2 at weeks 0/2 then every3 months	3 (100%)	3(100%)	NA (12-24)	IV
Narvaez, 2014[32]	SSc (9)	P	NA	9 (100%)	NA	NA	IV
Giuggioli, 2015[33]	SSc (6)	P	375 mg/m2 at weeks 0/1/2/3	3 (50%)	0 (0%)	30 (18-48)	IV
Fredi, 2015[29]	DM (2)	R	NA	1 (50)	0 (0%)	201.8	IV
Children							
Aggarwal, 2016[30]	DM (22)	RCT	0.575-1g/m2 at weeks 0/1	NA	1 (4%)	1.46	IB
Bader-Meunier, 2011[34]	DM (6)	R	2x500mg/m2 (n=3) 4x375 mg/m2 (n=3)	0 (0%)	0 (0%)	NA (20.2-36)	IV
Alhemairi, 2017[35]	DM (4)	R	NA	4 (100%)	1 (25%)	NA (36-60)	IV

DM: dermatomyositis, SSc: systemic sclerosis RCT: randomized controlled trial, P: prospective, R: retrospective, NA: not available

*according to modified Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation

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471 **Table 3. Characteristics of included studies evaluating the effect of bisphosphonates, surgery and physical therapies on calcinosis cutis improvement**

Name/year	Disease (N)	Study design	Drug	Dose regimen	Partial response, N (%)	Complete response, N (%)	Follow-up, mean (range), months	Level of evidence, grade*
Biphosphonates								
Adult								
Balin, 2012[28]	NA (2)	R	Etidronate	NA	1 (50%)	0 (0%)	NA	IV
Children								
Marco Puche, 2009[39]	DM (3)	R	Pamidronate	IV 1mg/kg/day at day 1, 2, 3 every3 months	3 (100%)	1 (33%)	42	IV
Tayfur, 2015[40]	DM (3)	R	Pamidronate	IV 1mg/kg/day every 3 months	2 (66%)	1 (33%)	84	IV
	DM (1)	R	Risedronate	PO 1.25 mg/day	1 (100%)	1 (100%)	84	IV
	DM (2)	R	Alendronate	PO 70mg/week	0 (0%)	0 (0%)	84	IV
Saini, 2016[41]	DM (6)	R	Alendronate	NA	4 (66%)	0 (0%)	22.32 (4.9-27.7)	IV
Surgery and physical therapies								
Adult								
Bottomley, 1996	SSc (6)	P	Carbon dioxyde laser	Range of power between 7-5 and 10 W	5 (83%)	NS	> 6	IV
Balin, 2012	NA (28)	R	Surgical excision		27 (96%)	22 (79%)	104	IV
	NA (1)	R	Low frequency ultrasound	NS	1 (100%)	0 (0%)	NA	IV
Blumhardt, 2016	SSc (4)	P	ESWT	1 day/week 3 weeks	4 (100%)	0 (0%)	3	IV
Sultant-Bichat, 2012	DM (1) SSc (2)	P	ESWT	1 day/3 weeks, 3 times	1 (33%)	0 (0%)	8	IV
Shetty, 2005	SSc (3)	P	Iontophoresis of acetic acid + ultrasound	3 d/ week, 3 weeks	0 (0%)	0 (0%)	0.75	IIB
Fahmy, 1998	SSc (15)**	P	Surgical excision (microdrilling)		12 (80%)	NA	0.1	IV

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R: retrospective, IV: intravenously, PO: Per mouth, NA: not available, DM: dermatomyositis, SSc: systemic sclerosis; ESWT: extracorporeal shock-wave therapy; *according to modified Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation. **Improvement in 12/15 digits in 10 treated patients.

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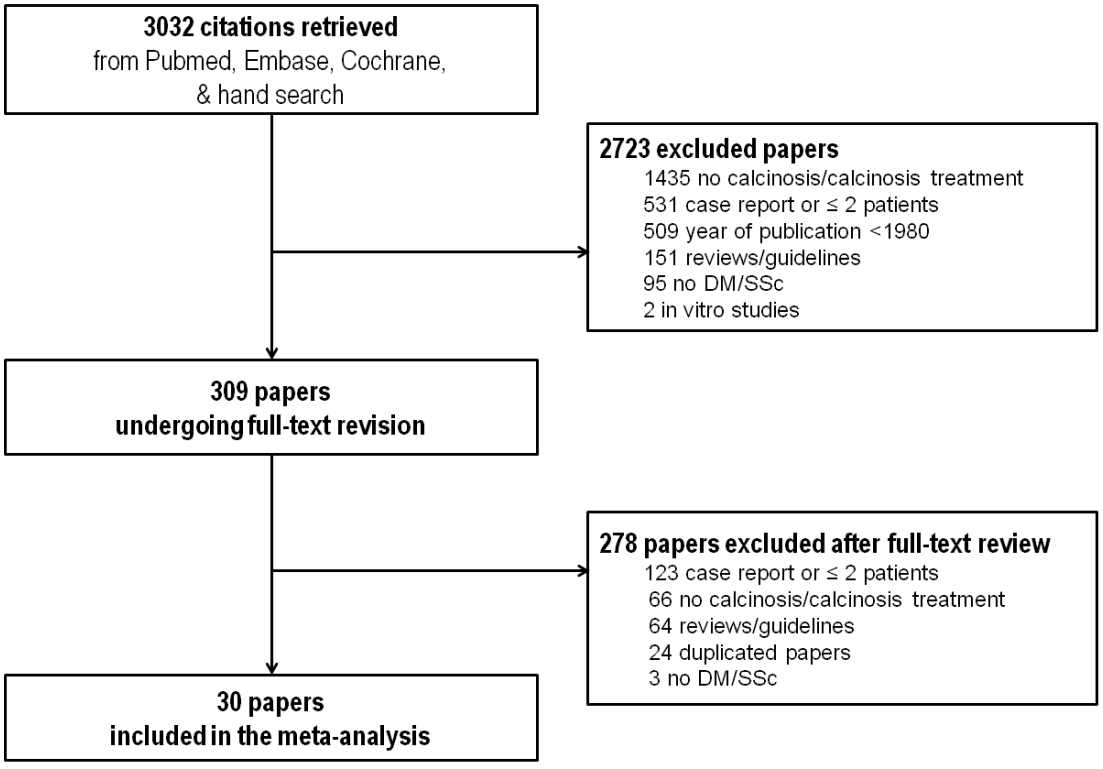
Table 4. Summary of available treatments for treating calcinosis cutis in DM and SSc patients

Drug/therapeutic class[ref]	Number of DM/SSc patients treated	Overall response rate (%)	Comments[ref] (level of evidence)	Grade of recommendation
Warfarin[20,26–29]	6/10 (NA=3)	0-66%	Should not be recommended (IB)	B
Diltiazem[10,28,29]	12/12 (NA=14)	0-64%	-May have a preventive effect[12] -Should be discussed in SSc patients and DM with Raynaud's phenomenon (IV)	C
Infliximab[29,36,38]	20/0	0-80%	May be discussed in DM patients (IV)	C
Abatacept[37]	4/0	100%	May be discussed in DM patients (IV)	C
Rituximab[29–35]	41/18	0-100%	May be discussed in DM and SSc patients	C
Biphosphonates[28,39–41]	15/0 (NA=2)	0-100%	May be discussed in DM patients (IV)	C
Intravenous immunoglobulins[29,42]	15/0	0-62%	May be discussed in DM patients (IV)	C
Minocyclin[28,52]	0/9 (NA=3)	33-88%	May be discussed in SSc patients (IV)	C
Colchicine[28,29]	(NA=16)	11-43%	May be discussed in DM and SSc patients (IV)	C
Cyclophosphamide[53]	14/0	69%	May be discussed in DM patients (IV)	C
Intravenous sodium thiosulfate[48,49]	4/3	0%	Should not be recommended (IV)	C
Topical* or intralesional sodium thiosulfate[29,50,51]	7/6	0-100%	May be discussed in DM and SSc patients (IV)	C
Surgical excision and physical therapies[28,47]	0/15 (NA=28)	80-96%	-May be discussed in DM and SSc patients (IV) -Carbon dioxide laser[43], low frequency ultrasound[28] and ESWT[44,45] may be alternative treatments to surgery (IV) -Iontophoresis of acetic acid + ultrasound[46] seems ineffective (IIB)	C C C

DM: dermatomyositis; SSc: systemic sclerosis; NA: DM or SSc patients but unspecified diagnosis; * including sodium metabisulfite


3032 citations retrieved
from Pubmed, Embase, Cochrane,
& hand search
2723 excluded papers
1435 no calcinosis/calcinosis treatment
531 case report or ≤ 2 patients
509 year of publication <1980
151 reviews/guidelines
95 no DM/SSc
2 in vitro studies
309 papers
undergoing full-text revision
278 papers excluded after full-text review
123 case report or ≤ 2 patients
66 no calcinosis/calcinosis treatment
64 reviews/guidelines
24 duplicated papers
3 no DM/SSc
30 papers
included in the meta-analysis

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- There is no evidence-based study focusing on the treatment of calcinosis cutis (CC) associated with systemic sclerosis and dermatomyositis

- Eleven therapeutic classes, surgery and physical treatments were identified as potential treatment for CC. Among them, low-dose warfarin should not be used (Level IB evidence) whereas rituximab may be a promising alternative (Level IV).

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