Calcinosis in systemic sclerosis: prevalence, clinical picture, management, complications

Abstract. This literature review summarizes current data on the epidemiology, pathophysiology, diagnosis and treatment of calcinosis cutis in patients with systemic sclerosis (SSc). The article deals with the analysis of observational studies of the frequency of calcinosis in SSc and associated clinical features, molecular research of potential pathogenetic mechanisms, clinical cases describing new diagnostic approaches and methods for the treatment of calcinosis. Calcinosis cutis is the deposition of insoluble calcium in the skin and subcutaneous tissues. Calcinosis is one of the main, poorly managed clinical problems in patients with SSc, affecting at least one quarter of patients with SSc. Calcification is associated with a longer disease duration, digital ulcers, acro-osteolysis, positive anticientromere and anti-topoisomerase antibodies. Although the pathogenesis of calcification is not fully known, there is evidence supporting the role of local chronic traumatization, chronic inflammation, vascular hypoxia and malregulation of bone matrix proteins as potential mechanisms for the development of this pathological condition in patients with SSc. The diagnosis can be established on the basis of clinical data or using plain X-ray. Several pharmacological treatment methods have been applied in patients with calcinosis with variable and not so significant results; in turn, surgical excision of calcium deposits remains mainstay of treatment. Keywords: calcifications; calcinosis cutis; systemic sclerosis; pathophysiology; clinical picture; management; review

Introduction

Calcinosis cutis refers to insoluble calcium deposits in the skin and subcutaneous tissue [1]. The most representative samples of calcinosis cutis associated with systemic sclerosis could be found on the Fig. 1 (a, b).

There are five calcinosis subtypes: dystrophic, metastatic, iatrogenic, idiopathic calcinosis, and calciliflaexia [3]. Metastatic calcification refers to calcium deposition in the normal skin or subcutaneous tissues, associated with an elevated calcium and/or phosphate levels in blood serum, often registered together with malignant neoplasm disintegration [3]. Dystrophic calcinosis is a subtype associated with autoimmune connective tissue diseases (ACTD), such as dermatomyositis (DM), and especially in its juvenile form (JDM), systemic sclerosis (SSc), mixed connective tissue disease, and more rarely, systemic lupus erythematosus (SLE) [4]. In the majority of cases, pathology afflicts upper limbs, especially fingers; calcinosis is associated with an acute pain syndrome, periodic flares of local inflammation and significant functional disorders. Although the detailed pathophysiology of calcinosis cutis is not completely clear, the generalized mechanism of dystrophic calcinosis presupposes deposition of calcined matter in the damaged tissue even if the calcium and/or phosphate levels in blood serum are normal [4]. This article reviews and summarizes the recent literature data, dealing with calcinosis prevalence, associated clinical factors, pathogenesis, diagnostics and treatment options suggested for dystrophic calcinosis accompanied by SSc.

Prevalence and associated clinical factors of calcinosis accompanied by SSc

The prevalence of calcinosis accompanied by SSc varies from 18 to 49 %. This wide margin may be attributed to different diagnostic methods, based on discrepant clinical
and/or X-ray data, as well as to differences in the patient population [5, 6]. This prevalence increases among pa-
tients with a long-term SSc history; with calcinosis usu-
ally manifesting itself after 10 or more years after diagno-
sis being established [4, 7]. Small monocentral studies
show that risk factors associated with calcinosis include
male gender, digital ulcers, digital scars, acroosteolysis,
telangiectasias, anticentromere antibodies (ACAs) and
antitopoisoaserase/Scl antibodies [8]. The international
cohort study recruiting 5218 patients confirmed calcino-
sis connection with digital ulcers, telangiectasias, ACAs,
and established the new predisposing factor – osteopo-
rosis [9].

Demographic features:
• Older age
• Longer disease duration
• Limited form of systemic sclerosis

Physical features:
• digital ulcers
• digital scars
• acroosteolysis
• telangiectasias
• heart damage
• gastrointestinal diseases
• lung hypertension
• arthritis
• osteoporosis

Autoantibodies:
• positive anticentromere antibodies (ACAs)
• positive antitopoisoaserase/Scl antibodies
• positive antircardioliipin antibodies

However, the recent studies demonstrate various cal-
cinosis clinical associations, depending on the studied
population group. It cast doubts on the earlier found pre-
dictors. In the monocentral US study recruiting 215 pa-
tients with SSc, calcinosis was associated with a limited
SSc form (LF-SSc) [10]; however, in the Mexican and
Malaysian cohorts it was associated with a diffuse SSc
form (DF-SSc) [6]. Antinuclear and anti- Scl-70 antibod-
ies are more prevalent in the Mexican calcinosis patients
than ACAs [6], and antitopoisoaserase (Scl-70) antibod-
ies served as calcinosis predictors in the cohort of 1305
SSc patients, according to the Canadian Scleroderma Re-
search Group (CSRG) register, including patients from
Canada and Mexico [11]. Furthermore, in the multici-
ental study of 1009 US Blacks with SSc there were no asso-
ciations found with skin form, male gender or ACAs [5].

Clinical picture
SSc-accompanied calcinosis manifests itself with sub-
cutaneous nodes on fingers or in the pressure sites, such
as elbows, knees or ischial tuberosities. Calcinosis is most
often afflicting hands and feet (65-83 %), proximal upper
limbs (27 %), knee joints or proximal lower limbs (10-
22%) and thighs (6,7 %) [6]. Calcinosis sites may occur
on the trunk, chest, buttocks and other occult places,
such as maxillary sinuses, spine and paravertebral tissues
[12]. Calcinosis may be accompanied by painful sensa-
tions, soft tissue swelling, ulcers with an aligned infec-
tion or deformations, especially at the hands, resulting in
significant functional limitations [12]. Patients may also
complain of whitish discharge, resembling toothpaste,
from the infection opening gate sites.

Diagnosis
Although calcinosis is easily palpated or even seen
during the objective examination, imaging diagnostic
techniques help corroborating the diagnosis in case of
subclinical complications. X-ray is a sensitive method for ascertaining calcinosis and is considered an imaging method of first line for ACTDs (Fig. 2-5).

X-ray point-based system of hand calcinosis evaluation was recently developed and suggested in order to standardize measurements of calcium deposit sizes for clinical and research purposes [14]. This point-based system considers the affected site, density, number and anatomical position of deposits to evaluate the degree of calcinosis, making characteristic expert (intra- and interexpert) evaluations of various conclusions’ reliability (Fig. 6, 7).

Another method of calcinosis categorization was suggested taking into account clinical and X-ray features of lesions’ form and structure [15]. This approach subdivides calcinosis into four subtypes: ‘mousse’, ‘stone’, ‘net’ and ‘plate’. Researchers show that ‘net’ requires the longest therapeutic duration (140 ± 22 days on average) while ‘stone’ calcinosis – the shortest (30 ± 12 days), in case this categorization has any clinical significance and predictive value [15].

There is an ever increasing number of evidence proving ultrasound (U/S) efficacy while evaluating the SSc-accompanied calcinosis. V. Freire et al. (2013) report that U/S’s sensitivity for calcinosis is 89 %, which is not significantly lower than that of X-ray [16]. The latest study of 10 SSc patients suggests that PDI could be used to reveal inflammations around the calcium deposits, identifying the lesion area and thus targeting the anti-inflammatory therapy [17]. Furthermore, U/S used for revealing microcalcificates in breast tissues, may also differentiate hydroxyapatite deposits typical for SSc from other calcificates [17].

Other experimental research methods include multidetector computed tomography (MDCT), serial two photon (STP) tomography and MRI. MDCT has a higher resolution and 3D capacities absent in the regular CT, and thus enables more precise evaluation of the degree and prevalence of calcinosis [18]. Fig. 8 compares calcinosis imaging techniques: standard X-ray, MDCT and 3-D MDCT. Diagnostics of 16 SSc patients with STP
tomography demonstrated a high efficacy of revealing calcinosis in subcutaneous tissue, fasciae, carpal canal and adjacent muscles [19]. MRI is similarly effective for revealing calcinosis deposits, ensuring a better imaging of swelling and/or inflammation of tissues, potentially pointing towards calcinosis [20].

**Pathophysiology of calcinosis**

Among all the calcinosis types, dystrophic is the best researched one in terms of its pathophysiology. There are several mechanisms suggested: chronic inflammation, vascular hypoxia, recurring trauma and bone matrix protein anomaly. High levels of 1, 6, 1β interleukins, tumor necrosis factor α (TNF-α) were revealed in JDM patients with calcinosis confirming the role of inflammation in this pathologic process [21].

Furthermore, a case-control study recruiting 90 SSc patients from the Australian cohort and 90 matched control patients dealt with levels and polymorphism of mannose binding lectin (MBL) and ficolin-2 in blood serum; these two being lectin complement pathway receptors. As a result, researchers found association between these specific markers of SSc patients and calcification along with vascular disorders. They also revealed that mannose binding lectin (MBL) was significantly higher in SSc patients with calcinosis, compared to SSc patients without calcinosis (2,1 vs. 0,8 mg/ml, p = 0,005), and in SSc patients with digital ulcers and scars (2,7 vs. 0,8 mg/ml, p = 0,007) [22].

According to a number of studies, vascular ischemia also promotes calcinosis. C.A.Davies et al. demonstrate an elevated expression of hypoxia-associated glucose transporter 1 (GLUT1) in the skin biopsy of SSc patients with calcinosis [23]. Several studies [9] also show that presence or history of digital ulcers [11] and/or acroosteolysis [6] predict calcinosis, underlining the role of ischemia. Another study shows vascular endothelial growth factor (VEGF), also known as a potential angiogenic factor induced by hypoxia, when activated, becomes associated with an increased osteoclast activity in SSc patients with acroosteolysis, 73 % of them diagnosed with calcinosis [24]. This hypoxia-induced osteoclast activity is a factor in calcinosis development and may explain the calcinosis-osteoporosis connection [10]. In a similar
way, it was established that expression of the ascertained oxidative stress markers, end products of the progressive glycation/peroxidation of lipids and their receptors was higher in SSc patients’ derma, especially if they had calcinosis, compared to the healthy controls [25].

Calcinosis is predominantly localized on the dominant upper limb and other distal sites, suggesting that recurrent trauma/strain also may contribute to its development [26]. It’s worth mentioning that the sites facing recurrent traumatization may be more susceptible due to compensatory angiogenesis disorder, characterized by the proliferative obliterating vasculopathy attending SSc [27]. C. A. Davies et al. also found an increased bone matrix protein expression, among them osteonectin and matrix gamma-carboxyglutamic acid (Gla)-containing protein (MGP), in the skin of SSc patients with calcinosis [23]. Those proteins take part in the ectopic calcification, activating osteonectin, calcification trigger, along with suppression and reduction of MGP inhibitors [28]. MGP should take its gamma-carboxylated form and bind to the bone morphogenic protein-2 in order to inhibit calcification. This carboxylated form is Vitamin K-dependent [28]. R. Wallin et al. suggested mechanisms according to which oxidative stress, a decisive factor for SSc-attending microvascular lesions, may inhibit Vitamin K and produce nongamma-carboxylated and inactive MGP, thus resulting in the unruly calcification [29]. Further studies are required to understand these mechanisms better and reveal other pathogenetic constructions, favoring SSc-attending calcinosis.

Treatment

General measures and supporting therapy

Calcinosis is an important therapeutic problem for SSc patients. General measures include improving blood flow in the limbs, avoiding traumatization, stress factors and exposure to cold. If there is a suspicion of infected calcinosis lesions, antibiotics with antistreptococcal and antistaphylococcal action, nonsteroidal anti-inflammatory drugs (NSAIDs) and even opioids for pain relief [30]. If calcinosis turns into ulcers, a standard wound dressing is required [31].

Drug medication

Several groups of drugs were suggested to manage calcinosis, however, their results and efficacy vary. Evidence confirming their effect is mainly received from small retrospective studies, series and single clinical cases (Table 1).

Calcium channel blockers

Calcium channel blockers (CCB) reduce intercellular calcium migration in the damaged tissues, impairing calcium foci production and crystallization. Diltiazem is the most widely used and studied CCB in terms of calcinosis management. Early studies show promising results with a daily Diltiazem dose of 240-480 mg [32-34], which was confirmed in the retrospective cohort study of 78 ACTD patients at the Mayo Clinic. Diltiazem was effective as a first-line therapy in 9 out of 17 patients [35]. However, a large retrospective study could not confirm a positive Diltiazem effect in 12 SSc patients receiving a daily dose of 180 mg from 1 to 15 years, according to X-ray data [36]. Observational study by the Canadian Scleroderma Research Group (CSRG), based on the 5 year period, did not reveal any significant association between CCB and calcinosis outcomes (odds ratio (OR) 0.9; 95% confidence interval (CI) 0.73-1.05). Only those patients whose disease lasted less than 5 years showed a lower risk of calcinosis with CCB (odds ratio (OR) 0.62; 95% confidence interval (CI) 0.45–0.86) [37].

Bisphosphonates

Bisphosphonates may be useful to treat calcinosis with an aim to achieve a reverse calcification by means of macrophage-induced anti-inflammatory cytokine in-

Fig. 8. Advanced hand calcinosis by a regular X-ray (a), MDCT (b) and 3-D reconstruction MDCT (c) (borrowed from [19])
hhibition and bone resorption rate decrease [38]. Single clinical studies describe improvement of calcinosis course in dermatomyositis (DM) adult patients [40] and JDM patients [39] with intravenous Pamidronate injections. In a similar manner, a series of cases showed a partial reduction of calcinosis when treated with alendronate in 6 out of 9 JDM patients [41]. A clinical case with LF-SSc patient describes calcinosis-induced calcific dissolution after 6 month therapy with Risedronate, also used for glucocorticoid-induced osteoporosis treatment [42]. Taking into account a lack of evidence-based studies, bisphosphonates’ efficacy for calcinosis treatments remains unclear.

**Warfarin**

Considering that Warfarin reduces matrix gamma-carboxyglutamic acid (Gla)-containing protein (MGP) and prevents its carboxylation, a number of studies were made into efficacy of Warfarin’s low doses to treat ACTD calcinosis [12]. In a series of clinical observations, among 3 SSc patients receiving Warfarin two of them had calcinosis dissolved after 1 year of treatment [43].

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**Table 1. Pharmacological treatment of systemic sclerosis-associated calcinosis**

| Medications                  | Action mechanisms                                                                 | Doses                                      | Patients responding to treatment/total number of treated patients | Reference               | Efficacy |
|------------------------------|----------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------------------|--------------------------|----------|
| **Calcium channel blockers** | Reduction of intracellular calcium migration into the damaged tissues and local macrophages | Diltiazem 240–480 mg per diem – 1–12 years | 4/4                                                              | Palmieri et al. [32]      | Moderate  |
|                              |                                                                                            | Diltiazem 120 mg per diem – 2 years        | 1/1                                                              | Dolan et al. [33]        | Low      |
|                              |                                                                                            | Diltiazem 240 mg per diem – 5 years        | 1/1                                                              | Farah et al. [34]        | Low      |
| **Bisphosphonates**          | Macrophage-induced anti-inflammatory cytokine suppression, calcium metabolism slow-down | Risedronate 10 mg – 6 months               | 1/1                                                              | Fujii et al. [42]        | Low      |
| **Warfarin**                 | Inhibiting calcium-binding gamma-carboxyglutamic acid                                  | 1 mg per diem – 1 year                     | 2/3                                                              | Cukierman et al. [43]    | Low      |
|                              |                                                                                            | 1 mg per diem – 18 months                  | 2/3                                                              | Berger et al. [44]       | Low      |
|                              |                                                                                            | 1 mg per diem – 7–28 months                | 0/1                                                              | Lassoued et al. [45]     | Low      |
| **Sodium thiosulphate (STS)**| Powerful antioxidant and vasodilator, also chelating and dissolving calcium deposits    | Local: 25% STS with zinc oxide              | 2/2                                                              | Barrio Diaz et al. [47]  | Moderate |
|                              |                                                                                            | Local: 25% sodium metabisulfite (SM)       | 1/1                                                              | Goosens et al. [48]      | Low      |
|                              |                                                                                            | Intrafocal: STS 2-3 grams per diem – 1 year | 2/2                                                              | Goosens et al. [48]      | Low      |
|                              |                                                                                            | Intrafocal: STS 12.5-275 mg- 1-4 times      | 5/5                                                              | Baumgartner-Nielsen et al. [49] | Low    |
|                              |                                                                                            | Intravenous: 20 grams per diem, 5 days a month, no less than 6 times | 0/1                                                              | Mageau et al. [68]       | Low      |
| **Anti-TNF-α**               | Inhibiting calcinosis inflammation                                                       | Infliximab 3 mg/kg intravenously at weeks 0, 2, and 6, every 8 weeks – 7 months | 1/1                                                              | Tosonidouu et al. [51]   | Low      |
| **Rituximab**                | Chimeric anti-CD20 antibody depleting B-lymphocytes                                     | 375 mg/m² intravenously weekly Nº 4         | 1/1                                                              | De Paula et al. [52]     | Low      |
|                              |                                                                                            | 375 mg/m² intravenously weekly Nº4          | 3/6                                                              | Giuggioli et al. [53]    | Low      |
|                              |                                                                                            | 1 gram intravenously Nº2 with 2-week interval, and after that every 6 months | 0/1                                                              | Hurabielle et al. [54]   | Low      |
blind placebo controlled study of 7 patients with ACTD and numerous subcutaneous calcificates shows a reduction of extraskeletal calcium absorption on total body scintigraphy with Technetium 99m-diphosphonate in 2 out of 3 SSc patients receiving a daily Warfarin’s dose of 1mg during 18 months [44]. A series of additional clinical cases demonstrate 2 out of 3 SSc patients having a diffuse calcinosis dissolved on physical examination held 1 year after low-dose Warfarin treatment [43]. However, there are completely opposite findings. In the Mayo Clinic study, 4 out of 19 ACTD patients with calcinosis, who took Warfarin for other indications, did not have any improvement or changes in calcinosis compared to patients who did not take Warfarin [35]. Another study involving 6 patients with diffuse calcinosis (one of them also having SSc) shows that a 14,6-month Warfarin treatment turned out ineffective: in 5 patients calcinosis even got worse [45]. It is true that there are concerns as to the fact that Warfarin may promote calcification due to the inadequately carboxylated MGP [12].

**Sodium thiosulphate**

Topical (localized), intrafocal and intravenous Sodium thiosulphate (STS) injection was also studied in terms of calcinosis treatment. There are data describing two cases of ulcerous dystrophic calcinosis resistant to local treatment, however responsive to the topical application of 25 % STS in combination with zinc oxide [46]. Four patients with calcinosis (two with SSc, two with DM) had a significant reduction of size, erythema and pains with topical application of 25 % Sodium metabisulfite (SM), STS’s metabolite. Researchers suggest that topical SM may dissolve calcium deposits and promote local vasodilation and wound healing [47]. J. Goossens et al. report two cases of STS being used as daily intrafocal injections in a dose of 1–3 g, which led to pain relief, improvement of function and a two-fold diminishing of focal size after 12 months of therapy [48]. A large number of clinical cases describe treatment of 8 calcinosis sites in 6 patients (5 of them with SSc, one with nephrogenic systemic fibrosis) by means of 12,5–275 STS injections of 150 mg/ml
for over 4 weeks. By the 4th and 12th week, lesions diminished by 67 and 90% respectively, all patients reporting pain relief and function restoring [49]. Another series of 4 clinical cases (LF-SSc, DM, JDM, SLE) demonstrates calcinosis being improved after 6 cycles of intravenous STS injections in all patients, but for one with LF-SSc [50]. Further studies of STS efficacy are required for evidence base, to prove it could be used as a treatment alternative.

**Biological agents**

There are data on Infliximab’s efficiency while treating overlap syndrome, i.e. SSc-myositis and refractory calcinosis. Infliximab’s dose of 3 mg/kg was injected intravenously during 0, 2 and 6th week, and later every 8 weeks. As a result, calcificates diminished and there were no deposits reported after 41 months when controlled by means of a CT series [51].

Most references on biological therapy against calcinosis focus on Rituximab (RTX). There is a description of one clinical case of RTX №4 (375 mg/m²) daily intravenous use. Researchers observed improvement or a complete dissolution of calcified lesions [52]. Furthermore, a series of clinical observations of 10 SSc patients treated with RTX for interstitial lung disease (ILD), skin fibrosis and/or arthritis show improvement and dissolution of calcinosis in 3 out of 6 patients [53]. However, the recent findings also demonstrate aggravation of calcinosis in a DF-SSc patient treated with RTX for ILD and arthritis [54]. Similarly, 2 patients receiving RTX had their calcinosis progressing after 6 and 12 months following treatment [55]. At the moment, RTX may not be recommended as a calcinosis treatment option due to a lack of successful controlled studies.

**Other medications**

In a series of clinical studies with 9 LF-SSc and calcinosis patients, a daily dose of 50 or 100 mg Minocycline during 3. 5 years on average resulted in a reduced acuity and inflammation, and insignificant diminishing of deposits sizes in 8 patients [56]. There are separate reports confirming efficacy of Ceftriaxone [57], Aluminium hydroxide [58], Triamcinolone acetonide injections [59], Colchicine [35, 60], and IV Immunoglobulin use [61] to treat SSc-associated calcinosis. A new, potentially efficient treatment was suggested considering the preliminary data of ‘Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma’ (PHAROS) study reporting improvement of calcinosis after 6 months of treatment for SSc-associated pulmonary arterial hypertension (PAH) and calcinosis in 2 patients, prescribed subcutaneous Treprostinil for PAH. This improvement was confirmed by X-ray data [62]. Oral Treprostinil is tested at present in a clinical study of patients with SSc and hand calcinosis (NCT02663895).

**Procedures**

According to a prospective study of 9 calcinosis patients (three of them with SSc), 3 rounds of extracorporeal shockwave lithotripsy (ESWL) every 3 weeks reduced the size of lesions and calcinosis-associated pain syndrome after 6 months [63]. A recent 12-week study reporting 3 weekly ESWL rounds, focused on calcinosis foci in 4 SSc patients, revealed a diminishing of lesion sizes in 3 patients and pain relief in 2 [64]. Laser tissue CO₂ vaporization enables perfect imaging and calcium deposit vaporization; this procedure was also attended by pain relief and functional improvement in SSc-calcinosis patients [65].

Patients with large, localized and symptomatic lesions, especially those located over tendons, vessels and nerves are subject to the surgical intervention [66]. At the Mayo Clinic, all 11 patients who had only a surgical removal of calcified foci, as well as 16 out of 17 patients having both pharmaceutical and surgical treatment, responded to it. By contrast, only 7 out of 19 patients, having only pharmaceutical treatment, showed any response [35]. Special methods, such as a curettage of calcinosis foci [66] or cytoreduction with a high-frequency micro-drill [67], effectively reduced painful sensations and disability of calcinosis patients; however, lesions tended to recur.

**Conclusions**

Calcinosis is a prevalent problem for SSc patients. Most often, it is associated with upper limb lesions, especially affecting fingers. Although its pathogenesis is yet unclear, there is evidence of such pathogenic mechanisms as chronic inflammation, vascular hypoxia, local traumatization and dysregulation of bone matrix proteins. There are no universal and effective treatment methods for SSc-associated calcinosis; however, certain data on pharmacological options were published, among them CCB, bisphosphonates, Warfarin and Sodium thiosulphate. Surgical removal of calcinosis foci remains the fundamental treatment strategy. New clinical trials are required to determine effectiveness of the existing and new calcinosis treatment options.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Кальциноз при системній склеродермі: поширеність, клініка, менеджмент, ускладнення

Лекції, огляди / Lectures, Reviews

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Кальциноз при системній склеродермі: поширеність, клініка, менеджмент, ускладнення

Резюме. У даному літературному огляді підсумована сучасні дані щодо епідеміології, патофізіології, діагностики та лікування шкірного кальцинозу у пацієнтів із системною склеродермією (ССД). Проведено аналіз обсерваційних досліджень, що описують частоту кальцинозу при ССД і асоційованих з ним клінічних ознак; молекулярних досліджень, що вивча-
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Кальциноз при системной склеродермии: распространенность, клиника, менеджмент, осложнения

Резюме. В данном литературном обзоре проанализированы современные данные, касающиеся эпидемиологии, патофизиологии, диагностики и лечения кожного кальциноза у пациентов с системной склеродермией (ССД). Проведен анализ обсервационных исследований, описывающих частоту кальциноза при ССД и ассоциированных клинических признаков; молекулярных исследований, изучающих потенциальные патогенетические механизмы; представлены клинические случаи, описывающие новые диагностические подходы и методы лечения кальциноза. Кожный кальциноз — это отложение нерастворимого кальция в коже и подкожных тканях. Кальциноз — одна из основных, трудно управляемых клинических проблем у пациентов с ССД, затрагивающая всю область медицины.

Ключевые слова: кальцификация; кальциноз кожи; системная склеродермия; патофизиология; клиника; менеджмент; обзор