BRIEF REPORT

THE EFFECT OF DILTIAZEM ON CALCINOSIS IN A PATIENT WITH THE CREST SYNDROME

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We describe a patient with a 23-year history of progressive calcinosis and features of the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) who was treated with diltiazem, 240 mg/day, for 5 years. No clinical exacerbation of calcinosis occurred during treatment. Radiographs showed no new lesions, and there was reduction in the size of the existing lesions. Bone scans revealed a progressive decrease in the uptake of the radionuclide by soft tissue foci. We propose that diltiazem may stop the progression of calcinosis by reducing the cellular calcium influx in affected tissues.

Calcinosis occurs occasionally in various connective tissue disorders, but it is a cardinal feature of a form of limited scleroderma, the CREST syndrome, which also includes Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (1). The subcutaneous calcium deposits may result in local pain, recurrent drainage of the lesions, and secondary infection. The mechanism that causes calcinosis in connective tissue diseases is not well understood. In the absence of any generalized disturbance in calcium or phosphorus metabolism, it is considered to be a dystrophic calcinosis, related to alterations in connective tissue which result in an increased affinity for calcium salts.

No reliable therapy for calcinosis is currently available. Systemic administration of steroids is generally ineffective (2,3); intralesional administration of steroids appears to produce some benefit in calcinosis confined to the skin (4,5). Chelating agents, such as disodium EDTA (2,3), and diphosphonates (6,7) have yielded unimpressive results in clinical trials. In a few patients, probenecid appears to be beneficial (8,9), and colchicine has been shown to suppress both the local and the systemic inflammation of calcinosis universalis in patients with chronic dermatomyositis (10). Recently, low-dose warfarin therapy was advocated for mild cases of calcinosis universalis (11,12), but it was ineffective for more advanced cases (13).

Long-term administration of verapamil, a calcium channel blocker, has been shown to ameliorate uremic nephrocalcinosis in subtotally nephrectomized rats (14), and previous work from our laboratory has demonstrated that prolonged treatment with diltiazem results in a 50% reduction in excess accumulation of calcium in muscle tissues of dystrophic hamsters (15). The drug prompted a beneficial trend in muscle function in children with Duchenne's muscular dystrophy (16). In the present investigation, we tested the hypothesis that prolonged administration of diltiazem may ameliorate the course of calcinosis in patients with the CREST syndrome.

Case report. The patient, a 38-year-old black woman, was first seen in June 1982. She had a history of progressive calcinosis, which had begun at age 15,

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Supported in part by USPHS Clinical Research Center grant RR-00211.

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Submitted for publication December 4, 1989; accepted in revised form March 7, 1990.

Figure 1. Photographs of the patient's forearms and hands, showing multiple areas of calcinosis.

with swollen fingers and a low-grade fever. Gradually, nodular lesions developed in her hands and, later, her elbows, feet, and buttocks. The lesions eventually acquired a hard, rock-like consistency. The disease course was progressive, and it was complicated by recurrent episodes of inflammation around the lesions, with extrusion of a white, pasty material.

Between 1982 and 1983, the patient's condition deteriorated, with frequent involvement of other areas of her body. A therapeutic trial with diltiazem was therefore conducted after obtaining the patient's (signed) informed consent. She was admitted to the Clinical Research Center of the University of Tennessee in April 1983 because of a 12-day history of the gradual onset of pain, swelling, and purulent drainage from a lesion on her left elbow. She had received a course of nafcillin prior to admission, but this provided no improvement.

She described symptoms of Raynaud's phenomenon, but denied having dysphagia or arthralgia. Her only other medical problem was a 5-year history of hypertension, which was controlled with hydrochlorothiazide, 25 mg, plus triamterene, 50 mg (Dyazide; Smith Kline & French, Philadelphia, PA). Her family history was negative for calcinosis and connective tissue disease. She denied tobacco, alcohol, or drug abuse.

Physical examination findings included a weight of 46 kg, height of 153 cm, temperature of 37°C, pulse rate of 100/minute and regular, and a blood pressure of 110/78 mm Hg. Prominent telangiectasias were present on the patient's face, neck, tongue, buccal mucosa, and the palms of both hands. There was slight tightness of the facial skin and marked sclerodactyly, but the skin elsewhere was unremarkable. There were hard deposits in the soft tissue, which were associated with hyperpigmentation, and were most prominent over pressure points, especially on the extensor surfaces of the upper extremities, the ulnar border of the forearms, and the fingers of both hands. In the lower extremities, the patient's knees, toes, and buttocks were particularly involved.

The size of the lesions varied from 6 cm (diameter) on the left elbow to a few millimeters on the fingers. The lesion on the left elbow was a raised mass fixed to the skin and the deep subcutaneous tissue, with multiple punctate sinuses and a large central sinus that measured 0.5 × 0.7 cm and discharged purulent material (Figure 1). It was slightly warm and tender, with a hard consistency, but with no signs of abscess formation. There was tapering of the patient's fingers and marked sclerodactyly. There were flexion contractures of her right index finger and left elbow (to 30°).

Initially, laboratory tests showed mild leukocytosis, anemia, and an elevated erythrocyte sedimentation rate, which became normal after the infection in

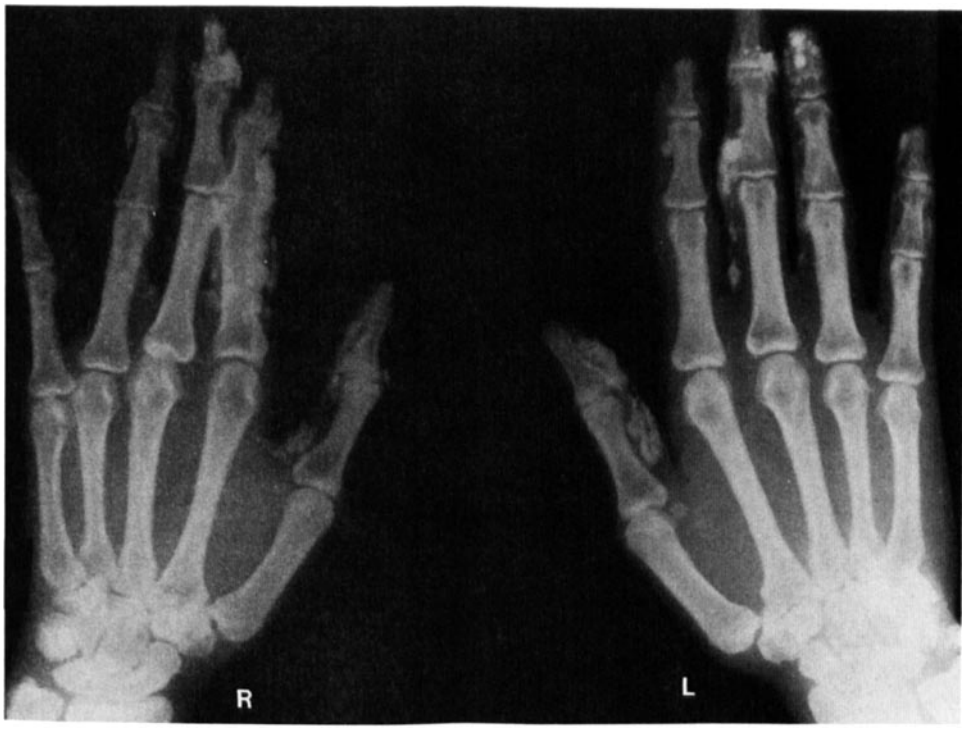

Figure 2. Posteroanterior radiographic view of the patient's hands, taken in 1983. There is extensive bilateral calcification, with periarticular and subcutaneous distribution. Sclerodactyly is present, with atrophy of the soft tissues of the fingertips bilaterally.

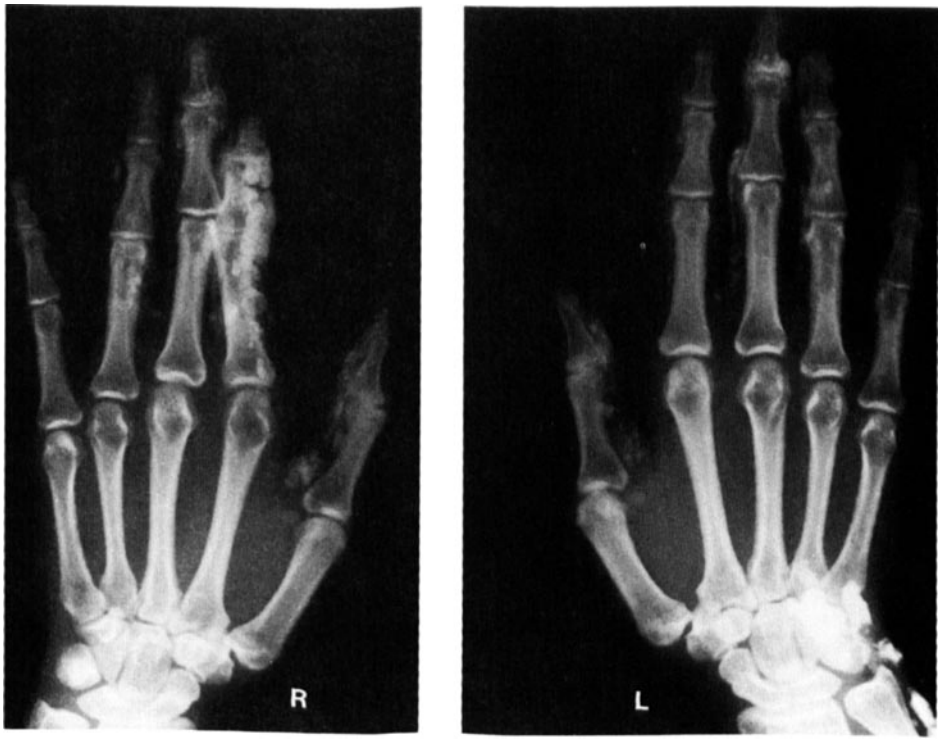

Figure 3. Posteroanterior radiographic views of the patient's hands, taken in 1988. There is a decrease in the extensive soft tissue calcification, compared with the 1983 films, at the left thumb, the proximal interphalangeal joint of the left middle finger, and in the soft tissues of the left index finger. There is almost complete resolution of the calcifications in the left distal fourth and fifth fingers, and in the right hand, calcifications have decreased significantly at the fourth proximal interphalangeal joint.

the elbow was successfully treated with a 10-day course of cephalexin. During the 5-year observation period, the anemia persisted, but these other laboratory values remained normal. Serum creatinine, calcium, phosphorus, sodium, potassium, total protein, albumin, uric acid, bilirubin, alkaline phosphatase, parathyroid hormone, and plasma cortisol concentrations were within normal limits during the 5-year period, as were the results of urinalysis and 24-hour urinary excretion of calcium and total protein levels. Thyroid function test results were normal.

Findings of single-photon bone densitometry studies of the patient's radius were within normal limits and remained unchanged over the 5 years of followup. Serum protein electrophoresis showed the following values: albumin 44% (normal 52–60), alpha-1 globulin 5.3% (normal 1.2–4.8), alpha-2 globulin 13.6% (normal 4.8–12), beta globulin 13.4% (normal 7.6–15.9), and gamma globulin 23.7% (normal 8.8–22.6). These values returned to normal during the 5-year period of treatment with diltiazem. Rheumatoid factor was positive at a titer of 1:20 (by latex agglutination) and the fluorescent antinuclear antibody test result was positive at a titer of 1:320, with nucleolar and speckled patterns. The anticentromere antibody test result was negative; however, antinucleolar antibodies (on HEp-2 cells) were positive at a dilution of 1:5,120. Results of chest radiographs, electrocardiograms, and a barium esophogram were normal.

Radiographs of the patient's extremities showed extensive calcific deposits in multiple pressure areas, including both elbows, forearms, and ischial tuberosities, as well as the hands and feet. Pericapsular calcifications, erosion of the distal phalangeal tufts, and soft tissue atrophy were identified on hand films (Figure 2). A ^{99m}Tc-methylene diphosphonate bone

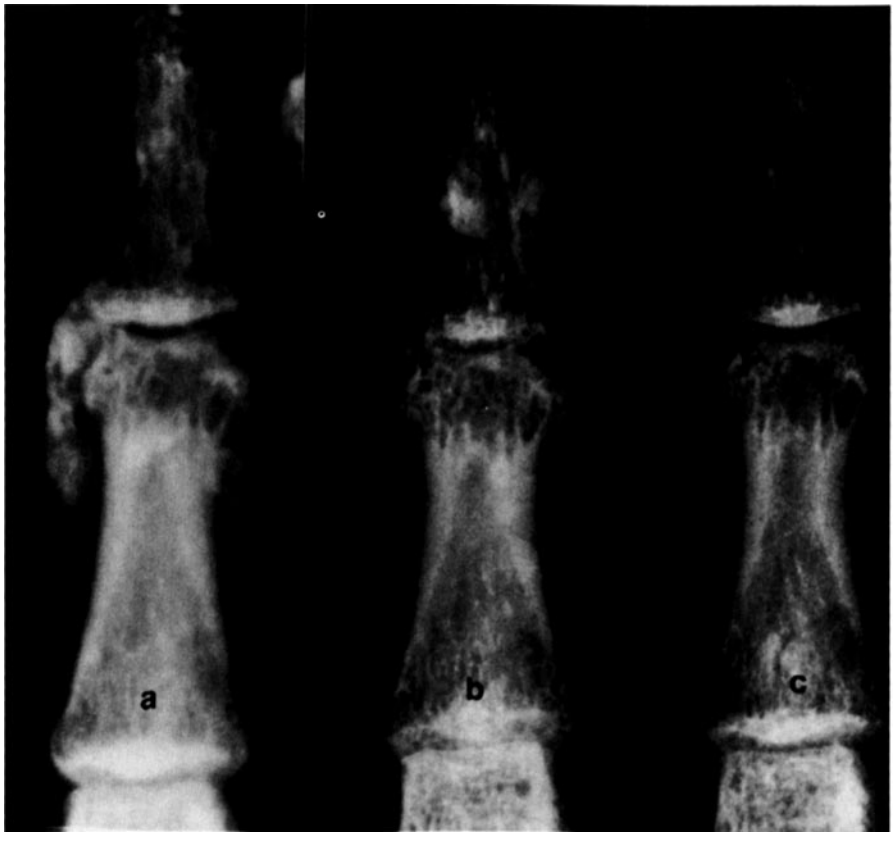

Figure 4. Posteroanterior radiographic views of the patient's right fourth finger. **a,** In 1983, there were extensive periarticular calcifications surrounding the distal interphalangeal joint. Note the small amorphous calcifications in the soft tissues adjacent to the distal phalanx and a small erosion of the tip of the phalanx, with punctate calcification. **b,** In 1984, the amorphous calcification surrounding the distal interphalangeal joint had decreased. **c,** In 1988, there was almost complete resolution of the periarticular calcifications.

scan demonstrated punctate soft tissue uptake around both thumbs, several fingers, and both gluteal areas beneath the ischial tuberosities. Uptake was apparent in the nonpunctate soft tissues of the extensor surfaces of both elbows and extending into the proximal forearms. The underlying bones were normal.

Treatment. The patient was started on a regimen of oral diltiazem, at a dosage of 120 mg/day. The dosage was gradually increased to 240 mg/day, which was given in 4 equal doses. Dyazide therapy was discontinued, and her blood pressure remained stable.

On yearly followup evaluations, there were no new exacerbations except for an episode of pain and swelling in the right patellar area following trauma and a second episode of pain in the dorsum of her right hand, which resolved promptly after a short course of indomethacin. After 1 year of treatment, her weight increased 8 kg, and remained stable thereafter. The calcific nodules and surrounding inflammatory changes became less prominent, with no evidence of new lesions.

Radiographs of her hands were obtained during her most recent hospital admission, in 1988. These revealed no progression in the overall extent of calcinosis, erosive changes, or sclerodactyly. In multiple areas of both hands, there was a significant decrease in the size of soft tissue calcifications, particularly in the periarticular areas of the fingers (Figure 3). The decreased size of the calcifications was best demonstrated in the right fourth finger (Figure 4) and left index finger (Figure 5). Yearly bone scans during the 5 years of treatment demonstrated a slight but progressive decrease in the abnormal soft tissue foci.

Discussion. Our observations indicate that prolonged treatment with diltiazem can be associated with the arrest and regression of widespread calcinosis in a

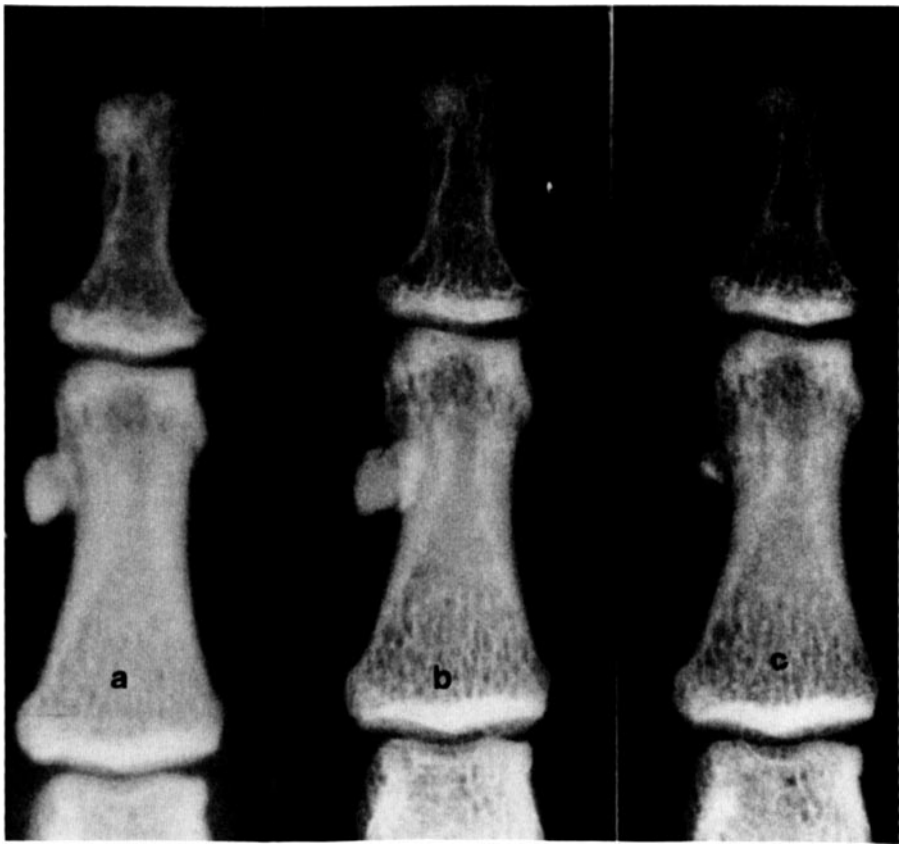

Figure 5. Posteroanterior radiographic view of the patient's left index finger. **a**, In 1983, there was globular calcification in the soft tissues of the radial side of the middle phalanx, with sclerosis of the lateral aspect of the tip of the distal phalanx and minimal erosion of the tuft. **b**, In 1984, there was a minimal increase in the size of the soft tissue calcification. **c**, In 1988, there was a marked decrease in the size of the globular calcification in soft tissues. The terminal phalangeal sclerosis and erosion of the tuft, however, persisted.

patient with the CREST syndrome. Inflammatory changes in the adjacent soft tissues also subsided in our patient. There was no evidence of an effect on the underlying connective tissue disease, except, perhaps, for improvement in the symptoms of Raynaud's phenomenon.

It is well known that the concentration of calcium in the cytosol of normal cells is approximately ten thousand times lower than that in the extracellular environment. Although small changes in intracellular calcium levels play a major role in normal cell activation, excessive accumulation of this cation could cause cell damage and, eventually, cell death. In many diseases, intracellular calcium accumulation may play a contributory role in pathogenesis. These include arterial hypertension, arteriosclerosis, hypoxia, acute pancreatitis, muscular dystrophy, and cystic fibrosis (17). Studies conducted in our laboratory have demonstrated that excessive calcium accumulation occurs both in animals and in humans with muscular dystrophies, and in Duchenne's muscular dystrophy, excessive accumulation of calcium precedes necrosis (18). We have also found that in dystrophic hamsters, maneuvers that reduce calcium influx into cells, such as parathyroid ablation (19), reduction of calcium influx by eliminating parathyroid hormone, a calcium agonist (20), or administration of the calcium antagonist diltiazem (15), results in a 50% reduction of the excess muscle calcium content. Prolonged administration of diltiazem also causes a trend toward clinical improvement (16) and the reduction of calcium-containing muscle fibers (21) in children with Duchenne's muscular dystrophy.

Our patient's response to diltiazem suggests that an increased influx of calcium into affected cells may play a role in the pathogenesis of calcinosis. The progressive resorption of established calcified lesions cannot be explained as a direct effect of treatment with diltiazem. However, it is conceivable that after the growth of the calcific deposit ceases, scavenging by macrophages at the periphery might contribute to its dissolution.

The present findings, if confirmed, may add a new indication for the use of calcium antagonists and may stimulate investigations on the pathophysiology of calcinosis, focusing on the role of cellular calcium metabolism.

Acknowledgments. We acknowledge the collaboration of Katherine Smull and Abbie Hinton in determination of bone densitometries, and the nursing staff at the Clinical Research Center and the technicians at the Departments of Radiology and Nuclear Medicine, University of Tennessee at Memphis, for skillful assistance. We also thank Renee Johnson for secretarial assistance.

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