Calcific Tendinopathy of the Rotator Cuff Tendons

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Abstract: Calcific tendinopathy (CT) of the tendons of the rotator cuff is common in white populations, with a reported prevalence varying from 2.7% to 22%, mostly affecting women between 30 and 50 years. Although CT shows a strong tendency toward self-healing by spontaneous resorption of the deposits, it does not always follow this typical pattern. The etiopathogenesis of CT is still unknown. Many pathogenetic theories have been proposed, and clinical associations between CT and diabetes and thyroid disorders have been reported. The choice of therapeutic approach should depend on the evolution of the condition.

Key Words: calcific tendinopathy, calcific deposits, tendons, review

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EPIDEMIOLOGY

Calcific tendinopathy (CT) of the tendons of the rotator cuff (RC) is common in white populations, with a reported prevalence varying from 2.7% to 22%, mostly affecting women between 30 and 50 years.[1–3] In 10% of patients, the pathology is bilateral.[1,4,5] The supraspinatus tendon is the most common site of occurrence: usually the deposits are located 1.5 to 2.0 cm away from the tendon's insertion on the greater tuberosity.[6] French investigators reported the presence of the calcific deposits in the supraspinatus tendon of 76%, in the infraspinatus tendon of 20%, whereas the subscapularis tendon in 6% of patients with CT.[7] Other investigators reported 66% of calcific deposits in the supraspinatus, 17% in the infraspinatus, and 17% in the subscapularis.[8]

Although CT shows a strong tendency toward spontaneous resorption of the deposits, it does not always follow this typical pattern, and this natural cycle may become blocked at any point. For instance, a symptomatic deposit may persist until it results in a tendon tear. According to an arthrographic study, an RC tear may coexist in approximately 25% of patients presenting with CT.[9] The choice of therapeutic approach should depend on the evolution of the condition.

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HISTORICAL REVIEW

CT is known under many names, including calcifying tendinitis, calcific tendinitis, calcified tendinitis, calcareous tendinitis, tendinosis calcarea, calcific periarthritis, and periarticular apatite deposit.[10] Some of the above terms emphasize the extra-articular location of the calcium deposit, others mention the nature of the compound found in the calcification. The more recent ones emphasize the active process that might explain the deposition, but all of them engender some confusion.

In 1907, Painter[11] was the first to describe the radiographic findings in patients with CT. Codman,[12] in the 1930s, proposed that degeneration of tendon fibers preceded calcifications. In 1941, the prevalence among asymptomatic individuals was reported to be 2.7% by Bosworth[1] based on a sample of 6061 volunteers from an insurance office. In 1978, Bateman[13] observed the calcific deposits in a typical area of hypovascularity, close to the tendon attachment named "zone of stress." More recently, Uhthoff and Loehr[6] proposed a progressive reactive calcification process to describe the disease cycle. In 1902, Harrington and Codman performed the first reported operative removal of a calcific deposits.[12] In the 1987, Ellman[14] first described the arthroscopic removal of calcific deposits.

CLINICAL FEATURES

During the deposition of calcium, patients may be pain free or mild symptomatic, and often if the pain worsens it is associated with resorption of the calcific deposits. However, the reason of the association of calcium deposition with the pain is still unknown.[6] Four different clinical presentations has been described[3,15,16]: (1) Acute form—it is characterized by severe pain, tenderness and functional disabilities, generally for 1 to 6 weeks. (2) Chronic recurrent form—it is characterized by the alternating of pain and well being. It may occur as such, without being preceded by an acute painful bout. Generally, it persists for 6 weeks to 6 months. (3) Persistent chronic form—it is characterized by presence of constant dull pain, with no phases of remission or exacerbation, which occurred for more than 6 months. (4) Totally asymptomatic deposits.

According to Bosworth,[1] clinical symptoms occur in 34% to 45% of patients in that calcifications are found. In a prospective study evaluating 1276 asymptomatic shoulders, the prevalence of RC calcification was 7.3%.[7] Clinical evolution of CT of RC often resolves spontaneously. Some investigators have described a different disease course with a longer duration of painful symptoms, and a reduction in the range of motion.[17,18] Wittenberg et al[19] and Chan et al[17] have attributed such poorer outcomes to cortical erosion. Osteolysis of the greater tuberosity is an uncommon, frequently misdiagnosed, and distinctive form of CT of the shoulder, associated with significantly lower clinical and

Table 1: Radiographic Classifications

A	**De Palma and Kruper Classification**
Type I	Fully, fleecy with ill-defined periphery
Type II	Homogeneous with clearly defined periphery
B	**French Arthroscopic Society classification**
Type A	Homogeneous calcification with well defined limits
Type B	Heterogeneous and fragmented calcification with well defined limits
Type C	Heterogeneous calcification with poorly defined limits and sometimes with a punctate appearance
Type D	Dystrophic calcification of the tendon insertion
C	**Gartner and Simons classification**
Type I	Sharply outlined and densely structured calcifications
Type II	Sharply outlined and inhomogeneous calcifications or homogenous with no defined border
Type III	Cloudy and transparent calcifications
D	**Patte and Goutallier classification**
Type I	Sharp and dense
Type II	Blunt and dense
Type III	Sharp and translucent
Type IV	Blunt and translucent

A, De Palma and Kruper classification; B, French Arthroscopic Society classification; C, Gartner and Simons classification; D, Patte and Goutallier classification.

functional outcome both before and after surgical treatment.[20] Chen et al[21] described 32 patients with adhesive capsulitis associated with CT of the supraspinatus.

Unfortunately there is no widely accepted clinical classification of the CT, and most clinical studies published do not identify the precise clinical phase when patients involved in the studies have been recruited.

IMAGING EVALUATION

Anteroposterior, internal, external rotation, and outlet view plain films are usually sufficient to diagnose CT of the shoulder, and they should be performed routinely. Various classifications based on the size of the deposits on radiographs, stage of the disease process, and its morphological appearance has been proposed. These classification systems may guide management, and should ensure that therapy is targeted according to the individual and to the stage of the disease. Four classifications have been reported. The classification by De Palma and Kruper[4] correlates the morphology of the calcified deposit on the RC tendons with both the patient's clinical situation and the stage of the disease. The French Arthroscopic Society classification[22] is based on the radiographic appearance of the calcium deposits. Patte and Goutallier[23] and Gartner and Simons[24] classifications concern only the morphological aspect of calcific deposits (Table 1).

Ultrasound (US) is as sensitive as plain radiography to identify the calcific deposits.[25] US Doppler imaging is useful to predict the evolution of CT,[26] but few studies have assessed the correlation between US findings and clinical expression in routine practice. Recently, Le Goff et al,[27] confirming results reported by Chiou et al,[26] showed that positive power Doppler signal within the calcific deposits were strongly associated with pain, and that the combination of US and power Doppler scans provides useful information on the likelihood of the calcification being

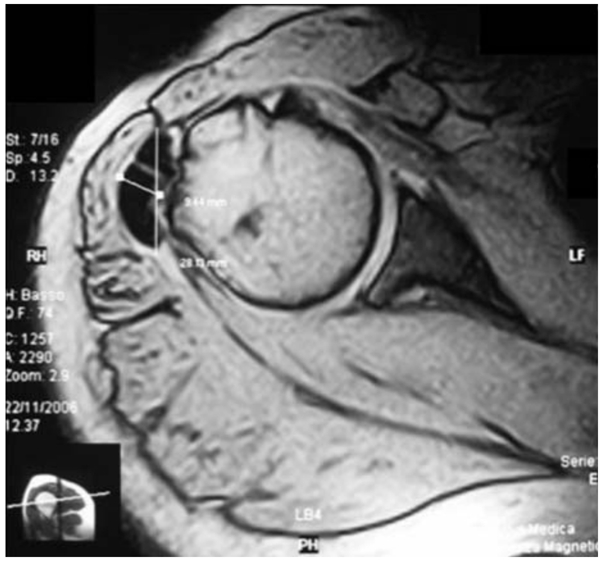

FIGURE 1. Magnetic resonance imaging in T1 of calcific tendinopathy of supraspinatus tendon >2 cm.

responsible for pain. Magnetic resonance imaging evaluation is not routinely indicated, but it could be useful to evaluate associated RC tears[28] (Fig. 1) and for CT with osteolysis of the great tuberosity.[20]

ETIOPATHOGENESIS

The etiopathogenesis of CT is still unknown, especially because it remains difficult to clarify the first steps, which induce calcium crystals deposition in the RC. These processes may well require several months, and biopsies of the pathologic cuff tendons are obtained only toward the end of the natural history of this disease, during the resorptive phase[29] and when patients are symptomatic. Two different theories have been developed. Codman[12] tried to explain the pathogenetic process of CT. He proposed that the degeneration of RC tendons caused by overuse or aging is the first step, which precedes calcifications.[12] Sandstrom[30] speculated that the degeneration of the tendon fibers was secondary to local ischemia, which favored deposition of calcifying material. Recently, 2 boys aged 3[31] and 13[32] years with CT have been reported: CT is difficult to explain in the pediatric age group. Mohr and Bilger[33] described the process as beginning with the necrosis of tenocytes with concomitant intracellular accumulation of calcium, often in the form of microspheroliths or psammomas.

After those investigators, Uhthoff and Loehr[6] and Uhthoff[29] hypothesized that a favorable environment permits an active process of cell-mediated calcification, usually followed by spontaneous phagocytic resorption. They proposed that the evolution of the condition could be divided into 3 distinct stages: precalcific, calcific, and postcalcific. In the precalcific stage, the site of predilection for calcification undergoes to fibrocartilaginous transformation. The calcific stage which is subdivided into 3 phases: formative, resting, and resorptive. In the postcalcific phase, the tendon heals with fiber realignment and resolution of the calcium deposit. These patterns may occur concomitantly in an individual patient. This hypothesis would explain the heterogeneity and pleomorphic nature of the disease.

Despite reasonable attempts to clarify the pathogenesis of CT, this issue is still unresolved, being based only on morphologic studies, which are not able to clarify the "first step." Attempts to reproduce the peculiar tendon environment of CT have used macrophages and synthetic apatite crystals and/or natural apatites.[34] This approach might help to understand how calcified material can be reabsorbed, but it does not explain all the pathologic processes involved in the development of the lesion. Possibly, better attempts to develop animal models for this disease would help this quest.

To make the picture more complicated, it is still unknown why CT is associated with diabetes and thyroid disorders.[35–37] More than 30% of patients with insulin-dependent diabetes have tendon calcification, and they are more likely to develop asymptomatic deposits.[38] Recently, Harvie et al[39] noted, in a retrospective cohort study of 102 consecutive patients with CT, a significantly higher prevalence of thyroid and estrogen hormones metabolism alterations compared with a control population. Earlier onset of the symptoms, longer natural history, and a higher proportion of patients undergoing surgery were evident in patients with associated endocrine disorders, suggesting a possible classification of the disease in idiopathic and endocrine-related forms.

BASIC SCIENCE

The histopathologic findings of CT have been extensively reported by Uhthoff and Loehr.[6] The precalcific stage is characterized by metaplasia of the tendinous tissue into fibrocartilage. Separated by chondrocytes and fibrocartilaginous tissue septae, calcium crystals are deposited primarily in matrix vesicles that coalesce to form large foci of calcification. The formative phase is characterized by multifocal calcific deposits, separated by fibrocollagenous tissue or fibrocartilage. The latter consists of easily distinguishable chondrocyte-like cells,[40] within a matrix showing various degrees of metachromasia. Inflammatory cells and vessels are notably absent. Archer again reported a lack of collagen type II and alkaline phosphatase in the pathologic regions, suggesting that the calcification process is not mediated through an endochondral transition. In contrast, the pathologic areas showed widespread labeling for chondroitin-4-sulphate/dermatan sulphate and intense pericellular localization of chondroitin-6-sulphate. In this formative phase, the deposits exhibit a chalk-like consistency.

The resting phase occurs when fibrocollagenous tissue borders the foci of calcification without evidence of inflammation, thereby indicating termination of deposition. The beginning of the resorptive phase is marked by the appearance of thin-walled vascular channels at the periphery of the deposit. Young mesenchymal cells, epithelioid cells, leukocytes, lymphocytes, macrophages, and multinucleated giant cells then surround the deposits in an attempt to phagocytose them. In this phase, the deposit appears a thick, creamy, toothpaste-like material that is often under pressure.

The last phase is the postcalcific stage. Granulation tissue with young fibroblast and newly formed capillaries can be found around the calcification, in contrast with well formed scars with vascular channels and maturing fibroblast following the long axis of the tendon fibers. Type III collagen has also been found using monoclonal antibodies, which confirmed the collagen neoformation.[6,38]

Nakase et al[41] clarified the nature of the multinucleated cells located near the calcium deposits. These were positive for cathepsin K protein and mRNA, and had a typical osteoclastis phenotype. The same research group 1 year later detected osteopontin only in the cells adjacent to the calcified area, identifying, morphologically, 2 distinct types of osteopontin positive cells, that is mononuclear fibroblastic cells and round-shaped multinuclear cells.[42]

What truly constitutes the calcific deposits is also still debated. The main components are water (H_2O), carbonate (CO_3), and phosphate (PO_4), and basic calcium phosphate crystals. Hamada et al[43] analyzed calcium deposits from patients with CT, and concluded that the deposits are consisted of carbonate apatite, and that hydroxyapatite, octacalcium phosphate, and tricalcium phosphate were not present. Rowe[44] described calcific deposits as appearing in 3 different forms. The first is a dry, powdery deposit in the chronic quiescent form. The second form is a soft, putty, or toothpaste deposit that may produce a mild chronic discomfort that is painful or aggravated by impinging in abduction under the acromion. The third is a milky or creamy collection that is usually under pressure. This corresponds to the acute, painful phase when the deposit is surrounded by inflammation and an acute synovitis or bursitis. Gartner and Simons[24] observed that the macroscopic differences of calcific deposits were not reflected in the mineralogical structure, and neither chemical compositional change nor a change in the crystal lattice was observed. They stated that no chemical dissolution process of the inorganic material was responsible for the resorption activity in the acute phase.

Few studies have been published on the proteins involved in the various phases of CT. We recently proposed a possible role for the bone morphogenetic proteins and transglutaminases. Bone morphogenetic proteins regulate calcification processes in bone, but their role in tendon repair has not been completely clarified yet.[45] Transglutaminases are a family of enzymes which are able to crosslink many extracellular proteins by a glutamine residue to a lysine residue of another protein chain in a reaction termed transamidation. They are expressed in almost all mammalian tissues, and their importance has been highlighted in wound healing and tissue repair, inflammation, and apoptosis.[46]

Although various proteins could be involved in the different phases, available data have mainly been obtained on the expression of specific genes.[47,48] Sengar et al[49] found an increased frequency of human leukocyte antigen-A1 in

TABLE 2. Single and Double Blind Randomized Studies on ESWT for the Treatment of CT, Actually Reported in the Literature

Authors	Patients	Follow-up
Daecke et al[60]	115	4 y
Gerdesmeyer et al[61]	144	12 mo
Cosentino et al[62]	70	15 mo
Pan et al[63]	60	12 wk
Pleiner et al[64]	43	7 mo
Peters et al[65]	90	6 mo
Albert et al[66]	80	16 wk
Hsu et al[67]	46	1 y
Hearnden A et al[68]	20	6 mo

CT indicates calcific tendinopathy; ESWT, extracorporeal shock wave therapy.

FIGURE 2. Preoperative radiograph of calcific tendinopathy of the supraspinatus tendon >2 cm.

patients with CT, indicating that they may be genetically susceptible to the condition. Gene expression studies could provide some further insights in CT, but few data are currently available on this disorder.[50,51]

THERAPY

Nonoperative Management

Nonoperative treatment is usually successful in up to 90% of patients.[52] Nonsteroidal anti-inflammatory drugs are widely prescribed to control pain, often before radiographic diagnosis of CT. Cimetidine in case series study has been used in chronic calcifying tendinitis of the shoulder, even though the mechanism by which cimetidine improves the symptoms is unknown.[53] Corticosteroid injections may have beneficial effects, but, although they are commonly used in the treatment of CT, there is no evidence that they promote resorption of the calcium deposits.[54,55] Physical therapy, with pendular movement and gentle exercises plus mobilizations of the shoulder if adhesive capsulitis is associated, should help to restore range of motion.[38] Hyperthermia has been report to be a safe option in the management of CT of the shoulder.[56]

The efficacy of therapeutic US in the treatment of CT is uncertain. The Cochrane Musculoskeletal Database Review of 26 trials found that both US and pulsed electromagnetic field therapy resulted in significant improvement in pain, compared with placebo.[57] However, a further meta-analysis of 35 randomized controlled trials found that only 2 studies supported the use of therapeutic US over placebo.[58]

Among the nonoperative modalities, extracorporeal shock wave therapy (ESWT) has been confirmed the treatment of choice in terms of reduction of pain, improvement in functional scores, and patient satisfaction without adverse effects. A recent systematic review confirmed that ESWT seems to be an effective therapy for the treatment of CT of the shoulder.[59] In Table 2, single and double blind randomized studies are reported.[60–68] Local complications after ESWT for CT as pain, reddening of the skin, hematoma, soft tissue swelling, transient bone edema, and nerve lesion have been described. They can occur from 7% to 19% of patients, and they are clearly dose dependent.[59] Two cases of osteonecrosis of the humeral head have also been reported.[69,70]

Operative Management

Approximately 10% of patients are resistant to conservative management, and surgical removal of the calcium deposit is necessary.[52] Surgery is indicated in patients with severe disabling symptoms, which have persisted for more than 6 months,[71,72] but there is no consensus regarding the optimal operative treatment. The key to successful management is to understand the natural history of the condition, thereby devising the optimum treatment based on the pathology.[52]

Needle lavage has been described as minimally invasive treatment in patients with an acutely painful shoulder during the resorptive phase, should help decompressing the tendon.[73–75] Treatment with modified US-guided fine needle technique is effective with a significant clinical response and greater precision.[76] Using US-guided needle puncture, Farin et al[77] found favorable results in more than 70% of patients. Galletti et al[78] found a

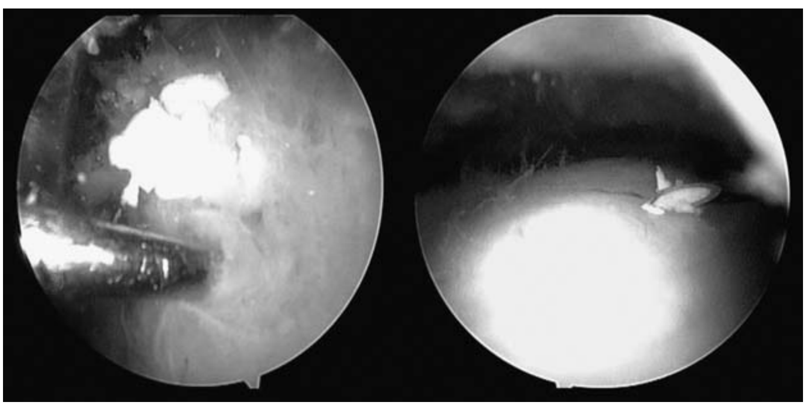

FIGURE 3. Arthroscopic treatment of calcific tendinopathy of the supraspinatus tendon >2 cm—intraoperative imaging.

FIGURE 4. Postoperative radiograph of a calcific tendinopathy of the supraspinatus tendon >2 cm, sutured with a metallic anchor.

reduction symptoms in nearly 90% of patients. Recently, Cacchio et al[79] reported good clinical results and disappearance of calcifications after 4 weeks using disodium ethylenediaminetetraacetic acid, without adverse effects. Ethylenediaminetetraacetic acid is widely used to sequester divalent and trivalent metal and mineral ions, currently used in chelation therapy.

Arthroscopic treatment of CT of the rotator cuff tears (RCT) has been described with successful results[5,80] (Figs. 2, 3), with outcomes equivalent to those of open procedures.[38] The importance of removing all of the calcium deposit is largely debate in literature. Many investigators stated that successful outcome seemed to be strongly related only to the absence of calcium deposits in the RCT. Jerosch et al[81] found that functional outcome was inversely related to the amount of calcification remaining. Hurt and Baker,[38] Porcellini et al,[72] and Rizzello et al[80] found better results when complete removal of the calcifications was achieved. Other investigators suggest that complete eradication of the calcium deposits are not necessary because the cell-mediated resorption can be initiated by the surgical incision of the affected tendon.[5,82]

Suture of the residual tendon lesions after removal of the deposits is not routinely performed as the natural process of the disease is self-healing of the tendon[38,82] if complete excision of the deposits is performed. No cuff tears were shown at US examination after the complete removal of calcific deposits at 5-year follow-up.[72] However, in another study, 7% of patients treated surgically still reported pain, and 25% of these patients showed a RC defect at US.[83] For these reasons, some surgeons recommend a primary side-to-side repair of RCT if the tear resultant defect after excision is large (Figs. 2, 4).[38,73] Suture of the RCT allows the patients to begin early rehabilitation. Acromioplasty is recommended only in patients with a type III acromion.[84]

CONCLUSIONS

Advances in the management of CT have been made more than in the knowledge about its etiopathogenesis. The process consists of a multifocal, cell-mediated calcification of a living tendon that is usually followed by spontaneous phagocytic resorption. After spontaneous, physiotherapeutic or surgical resolution of symptoms, the tendon usually returns to its normal structure. ESWT is highly effective in the chronic condition. A high prevalence of both autoimmune and hormone-related diseases have been reported in patients with CT. Many questions remain to be answered, including why the calcium precipitates within the tendon, what is the nature of the mechanism leading to calcium salt deposition, whether this mechanism is chemical or biological, where does the pain come from, and what induces the multinucleated cells to start the resorptive phase.[85] Further investigation will be necessary to clarify this process, and identify possible future therapeutic targets.

REFERENCES

1. Bosworth BM. Calcium deposits in the shoulder and subacromial bursitis: a survey of 12,122 shoulders. *J Am Med Assoc*. 1941;116:2477–2482.
2. Uthoff HK. Anatomopathology of calcifying tendinitis of the cuff. In: Gazielly DF, Gleyze P, Thomas T, eds. *The Cuff*. Paris: Elsevier; 1997:144–147.
3. Faure G, Daculis G. Calcified tendonitis: a review. *Ann Rheum Dis*. 1983;42:49–53.
4. De Palma AF, Kruper JS. Long-term study of shoulder joints afflicted with and treated for calcific tendinitis. *Clin Orthop*. 1961;20:61–72.
5. Ark JW, Flock TJ, Flatow EL, et al. Arthroscopic treatment of calcific tendinitis of the shoulder. *Arthroscopy*. 1992;8:183–188.
6. Uhthoff HK, Loehr JW. Calcific tendinopathy of the rotator cuff: pathogenesis, diagnosis, and management. *J Am Acad Orthop Surg*. 1997;5:183–191.
7. Clavert P, Sirveaux F. Shoulder calcifying tendinitis. *Rev Chir Orthop Reparatrice Appar Mot*. 2008;94(8 suppl):336–355.
8. Rhee YG, Kim YH, Park MS. Arthroscopic treatment in calcific tendinitis of the shoulder. *J Korean Shoulder Elbow Soc*. 2000;3:68–74.
9. Jim YF, Hsu HC, Chang CY, et al. Coexistence of calcific tendinitis and rotator cuff tear: an arthrographic study. *Skeletal Radiol*. 1993;22:183–185.
10. De Seze S, Welfling J. Tendinites calcifiantes. *Rhumatologie* 1970;22:5–14.
11. Painter C. Subdeltoid bursitis. *Boston Med Surg J*. 1907;156:345–349.
12. Codman EA. *The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or About the Subacromial Bursa*. Boston: Thomas Todd Co.; 1934.
13. Bateman JE. *The Neck and Shoulder*. Philadelphia: WB Saunders Co.; 1978.
14. Ellman H. Arthroscopic subacromial decompression: analysis of one- to three-year results. *Arthroscopy*. 1987;3:173–181.
15. Rotini R, Burgaro P, Antonioli D, et al. Algorithm for the treatment of calcific tendinitis in the rotator cuff: indications for arthroscopy and results in our experience. *Chir Organi Mov*. 2005;90:105–112.
16. Welfling J. The Calcifications of the shoulder: clinical diagnosis. *Rev Rhum Mal Osteoartic*. 1964;31:265–271.
17. Chan R, Kim DH, Millett PJ, et al. Calcifying tendinitis of the rotator cuff with cortical bone erosion. *Skeletal Radiol*. 2004;33:596–599.

18. Flemming DJ, Murphey MD, Shekitka KM, et al. Osseous involvement in calcific tendinitis: a retrospective review of 50 cases. *AJR Am J Roentgenol*. 2003;181:965–972.
19. Wittenberg RH, Rubenthaler F, Wolk T, et al. Surgical or conservative treatment for chronic rotator cuff calcifying tendinitisea matched-pair analysis of 100 patients. *Arch Orthop Trauma Surg*. 2001;121:56–59.
20. Porcellini G, Paladini P, Campi F, et al. Osteolytic lesion of greater tuberosity in calcific tendinitis of the shoulder. *J Shoulder Elbow Surg*. 2009;18:210–215.
21. Chen SK, Chou PH, Lue YJ, et al. Treatment for frozen shoulder combined with calcific tendinitis of the supraspinatus. *Kaohsiung J Med Sci*. 2008;24:78–84.
22. Mole D, Kempf JF, Gleyze P, et al. Results of endoscopic treatment of non-broken tendinopathies of the rotator cuff, II: calcifications of the rotator cuff. *Rev Chir Orthop Reparatrice Appar Mot*. 1993;79:532–541.
23. Patte CF, Goutallier D. Calcifications. *Rev Chir Orthop*. 1988;74:277–278.
24. Gartner J, Simons B. Analysis of calcific deposits in calcifying tendinitis. *Clin Orthop Relat Res*. 1990;254:111–120.
25. Papatheodorou A, Ellinas P, Takis F, et al. US of the shoulder: rotator cuff and non-rotator cuff disorders. *Radiographics*. 2006;26:23.
26. Chiou HJ, Chou YH, Wu JJ, et al. Evaluation of calcific tendonitis of the rotator cuff: role of color Doppler ultrasonography. *J Ultrasound Med*. 2002;21:289–295.
27. Le Goff B, Berthelot JM, Guillot P, et al. Assessment of calcific tendonitis of rotator cuff by ultrasonography: comparision between symptomatic and asymptomatic shoulders. *Joint Bone Spine*. 2010;77:258–263.
28. Loew M, Sabo D, Wehrle M, et al. Relationship between calcifying tendinitis and subacromial impingement: a prospective radiography and magnetic resonance imaging study. *J Shoulder Elbow Surg*. 1996;5:314–319.
29. Uhthoff HK. Calcifying tendinitis an active cell mediated calcification. *Virchows Arch Pathol Anat*. 1975;366:51–58.
30. Sandstrom C. Peridentinis calcarea: a common disease of middle life. Its diagnosis pathology and treatment. *AJR*. 1938;40:1–21.
31. Nutton RW, Stothard J. Acute calcific supraspinatus tendinitis in a three-year-old child: brief reports. *J Bone Joint Surg Br*. 1987;148–149.
32. Bittmann S. Calcific tendinitis of the supraspinatus tendon in children. *Klin Padiatr*. 2006;218:45–46.
33. Mohr W, Bilger S. Morphological basic structures of calcified tendinopathy and its importance in the pathogenesis. *Z Rheumatol*. 1990;49:346–355.
34. Cheung HS, Halverson PB, McCarty DJ. Release of collagenase neutral protease, and prostaglandins from cultured mammalian synovial cells by hydroxyapatite and calcium pyrophosphate dihydrate crystals. *Arthritis Rheum*. 1981;24:1338–1344.
35. Wright V, Haq AM. Periarthritis of the shoulder. I: aetiological considerations with particular reference to personality factors. *Ann Rheum Dis*. 1976;35:213–219.
36. Kaklamanis P, Rigas A, Giannatos J, et al. Letter: calcification of the shoulders and diabetes mellitus. *N Engl J Med*. 1975;293:1266–1267.
37. Mavrikakis ME, Drimis S, Kontoyannis DA et al. Calcific shoulder periarthritis (tendinitis) in adult onset diabetes mellitus: a controlled study. *Ann Rheum Dis*. 1989;48:211–214.
38. Hurt G, Baker CL. Calcific tendinitis of the shoulder. *Orthop Clin North Am*. 2003;34:567–575.
39. Harvie P, Pollard TC, Carr AJ. Calcific tendinitis: natural history and association with endocrine disorders. *J Shoulder Elbow Surg*. 2007;16:169–173.
40. Archer RS, Bayley JI, Archer CW, et al. Cell and matrix changes associated with pathological calcification of the human rotator cuff tendons. *J Anat*. 1993;182:1–12.
41. Nakase T, Takeuchi E, Sugamoto K, et al. Involvement of multinucleated giant cells synthesizing cathepsin K in calcified tendinitis of the rotator cuff tendons. *Rheumatology (Oxford)*. 2000;39:1074–1077.
42. Takeuchi E, Sugamoto K, Nakase T, et al. Localization and expression of osteopontin in the rotator cuff tendons in patients with calcifying tendinitis. *Virchows Arch*. 2001;438: 612–617.
43. Hamada J, Ono W, Tamai K, et al. Analysis of calcium deposits in calcific periarthritis. *J Rheumatol*. 2001;28:809–813.
44. Rowe CR. Calcific tendinitis. *AAOS Instr Course Lect XXXIV*. 1985;34:196–198.
45. Yee Lui PP, Wong YM, Rui YF, et al. Expression of chondro-osteogenic BMPs in ossified failed tendon healing model of tendinopathy. *J Orthop Res*. 2011;29:816–821.
46. Oliva F, Zocchi L, Codispoti A, et al. Transglutaminases expression in human supraspinatus tendon ruptures and in mouse tendons. *Biochem Biophys Res Commun*. 2009;379: 887–891.
47. Magra M, Maffulli N. Genetics: does it play a role in tendinopathy?. *Clin J Sport Med*. 2007;17:231–233.
48. Magra M, Maffulli N. Genetic aspects of tendinopathy. *J Sci Med Sport*. 2008;11:243–247.
49. Sengar DPS, McKendry RJ, Uhthoff HK. Increased frequency of HLA-A1 in calcifying tendinitis. *Tissue Antigenus*. 1987;29: 173–174.
50. Sweet HO, Green MC. Progressive ankylosis, a new skeletal mutation in the mouse. *J Hered*. 1981;72:87–93.
51. Zaka R, Stokes D, Dion AS, et al. P5L mutation in Ank results in an increase in extracellular inorganic pyrophosphate during proliferation and nonmineralizing hypertrophy in stably transduced ATDC5 cells. *Arthritis Res Ther*. 2006;8:1–13.
52. Lam F, Bhatia D, Van Rooyen K, et al. Modern management of calcifying tendonitis of the shoulder. *Curr Orthop*. 2006;20:446–452.
53. Yokoyama M, Aono H, Takeda A, et al. Cimetidine for chronic calcifying tendinitis of the shoulder. *Reg Anesth Pain Med*. 2003;28:248–252.
54. Uhthoff HK, Sarkar K. Calcifying tendinitis. In: Rockwood CR Jr, Matsen FA III, editors. *The shoulder, vol. 2*. Philadelphia: WB Saunders; 1990: 774–790.
55. Noel E, Carillon Y, Gaillard T, et al. Needle aspiration irrigation in calcifying tendinitis of rotator cuff. In: Gazielly DF, Gleyze PTT, eds. *The cuff*. Paris: Elsevier; 1997; 152–157.
56. Di Cesare A, Giombini A, Dragoni S, et al. Calcific tendinopathy of the rotator cuff: conservative management with 434 Mhz local microwave diathermy (hyperthermia): a case study. *Disabil Rehabil*. 2008;30:1578–1583.
57. Green S, Buchbinder R, Hetrick S. Physiotherapy interventions for shoulder pain. *Cochrane Database Syst Rev*. 2003:CD004258.
58. Robertson VJ, Baker KG. A review of therapeutic ultrasound: effectiveness studies. *Phys Ther*. 2001;81:1339–1350.
59. Mouzopoulos G, Stamatakos M, Mouzopoulos D, et al. Extracorporeal shock wave treatment for shoulder calcific tendonitis: a systematic review. *Skeletal Radiol*. 2007;36: 803–811.
60. Daecke W, Kusnierczak D, Loew M. Long-term effects of extracorporeal shockwave therapy in chronic calcific tendonitis of the shoulder. *J Shoulder Elbow Surg*. 2002;11:476–480.
61. Gerdesmeyer L, Wagenpfeil S, Haake M, et al. Extracorporeal shock wave therapy for the treatment of chronic calcifying tendonitis of the rotator cuff: a randomized controlled trial. *JAMA*. 2003;290:2573–2580.
62. Cosentino R, De Stefano R, Selvi E, et al. Extracorporeal shock wave therapy for chronic calcific tendinitis of the shoulder: single blind study. *Ann Rheum Dis*. 2003;62:248–250.
63. Pan PJ, Chou CL, Chiou HJ, et al. Extracorporeal shock wave therapy for chronic calcific tendinitis of the shoulders: a functional and sonographic study. *Arch Phys Med Rehabil*. 2003;84:988–993.
64. Pleiner J, Crevenna R, Langenberger H, et al. Extracorporeal shockwave treatment is effective in calcific tendonitis of the shoulder: a randomized controlled trial. *Wien Klin Wochenschr*. 2004;116:536–541.

65. Peters J, Luboldt W, Schwarz W, et al. Extracorporeal shock wave therapy in calcific tendinitis of the shoulder. *Skeletal Radiol*. 2004;33:712–718.
66. Albert JD, Meadeb J, Guggenbuhl P, et al. High-energy extracorporeal shock-wave therapy for calcifying tendinitis of the rotator cuff: a randomised trial. *J Bone Joint Surg Br*. 2007;89:335–341.
67. Hsu CJ, Wang DY, Tseng KF, et al. Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. *J Shoulder Elbow Surg*. 2008;17:55–59.
68. Hearnden A, Desai A, Karmegam A, et al. Extracorporeal shock wave therapy in chronic calcific tendonitis of the shoulder—is it effective? *Acta Orthop Belg*. 2009;75:25–31.
69. Durst HB, Blatter G, Kuster MS. Osteonecrosis of the humeral head after extracorporeal shock-wave lithotripsy. *J Bone Joint Surg Br*. 2002;84:744–746.
70. Liu M, Chao M, Hsieh Y, et al. Humeral head osteonecrosis after extracorporeal shock-wave treatment for rotator cuff tendinopathy: a case report. *J Bone Joint Surg Am*. 2006;88: 1353–1356.
71. Jerosch J, Strass JM, Schmiel S. Arthroscopic treatment of calcific of the shoulder. *J Shoulder Elbow Surg*. 1998;1:30–37.
72. Porcellini G, Paladini P, Campi F, et al. Arthroscopic treatment of calcifying tendinitis of the shoulder: clinical and ultrasonographic follow-up findings at two to five years. *J Shoulder Elbow Surg*. 2004;13:503–508.
73. Giacomoni P, Siliotto R. Echo-guided percutaneous treatment of chronic calcific tendinitis of the shoulder. *Radiol Med*. 1999;98:386–390.
74. De Zordo T, Ahmad N, Odegaard F, et al. US-guided therapy of calcific tendinopathy: clinical and radiological outcome assessment in shoulder and non-shoulder tendons. *Ultraschall Med*. 2011;32:117–123.
75. Lee KS, Rosas HG. Musculoskeletal ultrasound: how to treat calcific tendinitis of the rotator cuff by ultrasound-guided single-needle lavage technique. *AJR Am J Roentgenol*. 2010;195:638.
76. Aina R, Cardinal E, Bureau NJ, et al. Calcific shoulder tendinitis: treatment with modified US-guided fine-needle technique. *Radiology*. 2001;221:45–61.
77. Farin PU, Rasanen H, Jaroma H, et al. Rotator cuff calcifications: treatment with ultrasound-guided percutaneous needle aspiration and lavage. *Skeletal Radiol*. 1996;25: 551–554.
78. Galletti S, Magnani M, Rotini R, et al. The echo-guided treatment of calcific. *Chir Organi Mov*. 2004;89:319–323.
79. Cacchio A, De Blasis E, Desiati P, et al. Effectiveness of treatment of calcific tendinitis of the shoulder by disodium EDTA. *Arthritis Rheum*. 2009;61:84–91.
80. Rizzello G, Franceschi F, Longo UG, et al. Arthroscopic management of calcific tendinopathy of the shoulder: do we need to remove all the deposit? *Bull NYU Hosp Jt Dis*. 2009;67:330–333.
81. Jerosch J, Strauss JM, Schmiel S. Arthroscopic treatment of calcific tendinitis: how important to remove it? *Arthroskopie*. 1996;9:241–245.
82. Gazielly DF, Bruye're G, Gleyze P, et al. Open acromioplasty with excision of calcium deposits and tendon suture. In: Gazielly DF, Gleyze P, Thomas T, eds. *The cuff*. Paris: Elsevier; 1997;172–175.
83. Seil R, Litzenburger H, Kohn D, et al. Arthroscopic treatment of chronically painful calcifying tendinitis of the supraspinatus tendon. *Arthroscopy J Arthrosc Rel Surg*. 2006;22: 521–527.
84. Neer CS, II. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *J Bone Joint Surg Am*. 1972;5:441–450.
85. Oliva F, Barisani D, Grasso A, Maffulli N. Gene expression analysis in calcific tendinopathy of the rotator cuff. *European Cells and Materials*. 2011;21:548–557.