Calcific Tendinopathy of the Rotator Cuff Tendons

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Abstract

Calcific tendinopathy (CT) of the tendons of the rotator cuff (RC) is common in Caucasian 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 aetiopathogenesis of calcific tendinopathy 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.

Keywords:

Calcific Tendinophaty, Calcific Deposits, tendons, Review.

Epidemiology

Calcific tendinopathy (CT) of the tendons of the rotator cuff (RC) is common in Caucasian populations, with a reported prevalence varying from 2.7% to 22%, mostly affecting women between 30 and 50 years.[1,2,3] 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 1.5–2.0 cm away from the tendon's insertion on the greater tuberosity.[6] French authors reported the presence of the calcific deposits in the supraspinatus tendon of 76%, in the infraspinatus tendon of 20%, while the subscapularis tendon in 6% of patients with CT.[7] Others authors 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 is results in a tendon tear. According to an arthrographic study, a rotator cuff 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.

Historical review

Calcific tendinopathy is known under many names, including calcifying tendinitis, calcific tendinitis, calcified tendinitis, calcareous tendinitis, tendinosis calcarea, calcific periarthritis, periarticular apatite deposit[10]. Some of the above terms emphasise the extra-articular location of the calcium deposit, others mention the nature of the compound found in the calcification. The more recent ones emphasise the active process that might explain the deposition, but all of them engender some confusion. In 1907, Painter was the first to describe the radiographic findings in patients with calcific tendinopathy.[11] Codman, in the 1930s, proposed that degeneration of tendon fibers preceded calcifications.[12] In 1941, the prevalence among asymptomatic individuals was reported to be 2.7% by Bosworth based on a sample of 6061 volunteers from an insurance office.[1] In 1978, Bateman observed the calcific deposits in a typical area of hypovascularity, close to the tendon attachment named "zone of stress".[13] More recently, Uhthoff and Loehr proposed a progressive reactive

calcification process to describe the disease cycle.[6] In 1902, Harrington and Codman performed the first reported operative removal of a calcific deposits.[12] In 1987, Ellman first described his removal arthroscopic technique followed by acromioplasty.[14]

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 and coworkers, clinical symptoms occur in 34% to 45% of patients in that calcifications are found.[1] 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 authors 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 functional outcome both before and after surgical treatment.[20] Chen et al described 32 patients with adhesive capsulitis associated with calcific tendinopathy of the supraspinatus.[21]

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 rotator cuff tendons with both the patient's clinical situation and the stage of the disease. The French Arthroscopic Society classification[23] is based on the radiographic appearance of the calcium deposits. Patte-Goutallier[24] and Gartner-Simons[25] classifications concern only the morphological aspect of calcific deposits (Table I).

Ultrasound (US) is as sensitive as plain radiography to identify the calcific deposits.[26] US Doppler imaging is useful to predict the evolution of CT[27], but few studies have assessed the correlation between US findings and clinical expression in routine practice. Recently Le Goff,[28] confirming results reported by Chiou,[27] 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 responsible for pain. Magnetic resonance imaging evaluation is not routinely indicated, but it could be useful to evaluate associated RC tears[29] (Fig. 1) and for CT with osteolysis of the great tuberosity.[20]

Aetiopathogenesis

The aetiopathogenesis 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 towards the end of the

natural history of this disease, during the resorptive phase[30] and when patients are symptomatic. Two different theories have been developed. Codman 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[31] speculated that the degeneration of the tendon fibers was secondary to local ischemia which favoured deposition of calcifying material. Recently, two boys aged three[32] and 13[33] with CT have been reported: CT is difficult to explain in the paediatric age group. Mohr and Bilger described the process as beginning with the necrosis of tenocytes with concomitant intracellular accumulation of calcium, often in the form of microspheroliths or psammomas.[34]

After those authors, Uhthoff and coworkers hypothesized that a favorable environment permits an active process of cell-mediated calcification, usually followed by spontaneous phagocytic resorption.[6,30] They proposed that the evolution of the condition could be divided into three distinct stages: pre-calcific, calcific, and post-calcific. In the pre-calcific stage, the site of predilection for calcification undergoes to fibrocartilaginous transformation. The calcific stage which is subdivided into three phases: formative, resting, and resorptive. In the post-calcific 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 calcific tendinophaty have employed macrophages and synthetic apatite crystals and/or natural apatites.[35] This approach might help to understand how calcified material can be reabsorbed, but it does not explain all the pathological 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.[36,37,38] More than 30% of patients with insulin-dependent diabetes have tendon calcification, and they are more likely to develop asymptomatic deposits.[39] Recently, Harvie et al. noted, in a retrospective cohort study of 102 consecutive patients with CT, a significantly higher prevalence of thyroid and estrogen hormones metabolism alterations compared to a control population.[40] 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 histopathological findings of CT have been extensively reported by Uhthoff.[6] The precalcific stage is characterised 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,[41] 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 pathological regions, suggesting that the calcification process is not mediated through an endochondral transition. In contrast, the pathological areas showed widespread labelling for chondroitin-4-sulphate/dermatan sulphate and intense pericellular localisation 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, leucocytes, 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 post-calcific 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.[6,39]

Nakase et al 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.[42] The same research group one year later detected also osteopontin only in the cells adjacent to the calcified area, identifying, morphologically, two distinct types of osteopontin positive cells, i.e. mononuclear fibroblastic cells and round-shaped multinuclear cells.[43]

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 and coworkers analyzed calcium deposits from patients with CT, and concluded that the deposits are composed of carbonate apatite, and that hydroxyapatite, octacalcium phosphate, and tricalcium phosphate were not present.[44] Rowe described calcific deposits as appearing in three different forms.[45] 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 et al.[25] observed that the macroscopic differences of calcific deposits was 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 (BMPs) and Transglutaminases (TGs). BMPs regulate calcification processes in bone, but their role in tendon repair has not been completely clarified yet.[48] TGs are a family of enzymes which are able to crosslink many extracellular proteins via 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.[49] Although various proteins could be involved in the different phases, available data have mainly been obtained on the expression of specific genes.[50,51] Sengar et al. found an increased frequency of HLA-A1 in patients with calcific tendinopathy, indicating that they may be genetically susceptible to the condition.[52] Gene expression studies could provide some further insights in calcific tendinopathy, but few data are currently available on this disorder.[53,54]

Therapy

Non operative management

Non-operative treatment is usually successful in up to 90% of patients.[55] NSAIDs 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.[56] 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.[57,58] 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.[39] Hyperthermia has been report to be a safe option in the management of CT of the shoulder.[59]

The efficacy of therapeutic ultrasound in the treatment of CT is uncertain. The Cochrane Musculoskeletal Database Review of 26 trials found that both ultrasound and pulsed electromagnetic field therapy resulted in significant improvement in pain, compared to placebo.[60]

However, a further meta-analysis of 35 randomised controlled trials found that only 2 studies supported the use of therapeutic ultrasound over placebo.[61]

Among the non-operative modalities, extracorporeal shock wave therapy (ESWT) has been confirmed the treatment of choice in terms of reduction of pain, improvement in functional scores, 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.[62] In Table II, single and double blind randomised studies are reported.[63,64,65,66,67,68,69,70,71] Local complications after ESWT for CT as pain, reddening of the skin, haematoma, 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.[62] Two cases of osteonecrosis of the humeral head have also been reported.[72,73]

Operative management

Approximately 10% of patients are resistant to conservative management, and surgical removal of the calcium deposit is necessary.[55] Surgery is indicated in patients with severe disabling symptoms which have persisted for more than 6 months,[74,75] 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.[55]

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.[76,77,78] Treatment with modified ultrasound-guided fine needle technique is effective with a significant clinical response and greater precision.[79] Using ultrasound-guided needle puncture, Farin et al found favourable results in more than 70% of patients.[80] Galletti found a reduction symptoms in nearly 90% of patients.[81] Recently, Cacchio et al reported good clinical results and disappearance of calcifications after 4 weeks using disodium EDTA, without adverse effects.[82] EDTA is widely used to sequester divalent and trivalent metal and mineral ions, currently used in chelation therapy.

Arthroscopic treatment of CT of the RCT has been described with successful results [5,83] (Fig. 2, 3), with outcomes equivalent to those of open procedures.[39] The importance of removing all of the

calcium deposit is largely debate in literature. Many authors stated that successful outcome appeared to be strongly related only to the absence of calcium deposits in the RCT. Jerosch et al found that functional outcome was inversely related to the amount of calcification remaining.[84] Hurt and Baker,[39] Porcellini et al [75] and Rizzello et al [83] found better results when complete removal of the calcifications was achieved. Other authors 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.[5,85]

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[39,85] if complete excision of the deposits is performed. No cuff tears were shown at ultrasound examination after the complete removal of calcific deposits at five years follow-up.[75] However, in another study 7% of patients treated surgically still reported pain, and 25% of these patients showed a RC defect at US.[86] For these reasons, some surgeons recommend a primary side to side repair of RCT if the tear resultant defect following excision is large (fig. 2 and fig. 4).[39,76] Suture of the RCT allows the patients to begin early rehabilitation. Acromioplasty is recommended only in patients with a type III acromion.[87]

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. Further

investigation will be necessary to clarify this process, and identify possible future therapeutic targets.

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Tables

Table I

A	De Palma and Kruper classification
Type I	Fully, fleecy with ill-defined periphery
Type II	Homogeneous with clearly defined periphery

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

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

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

Table I: Radiographic classifications: A- De Palma and Kruper classification; B- French Arthroscopic Society classification; C- Gartner and Simons classification; D- Patte and Goutallier classification

Table II

Authors	**Year**	**Patients**	**Follow-up**
Daecke W et al[61]	2002	115	4 years
Gerdesmeyer L et al[62]	2003	144	12 months
Cosentino R et al.[63]	2003	70	15 months
Pan PJ et al.[64]	2003	60	12 weeks
Pleiner J et al.[65]	2004	43	7 months
Peters J et al.[66]	2004	90	6 months
Albert JD et al[67]	2007	80	16 weeks
Hsu CJ et al.[68]	2008	46	1 year
Hearnden A et al.[69]	2009	20	6 months

462 Table II: Single and double blind randomised studies on ESWT for the treatment of CT actually
463 reported in the literature.
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465

Figures Legends

Figure 1

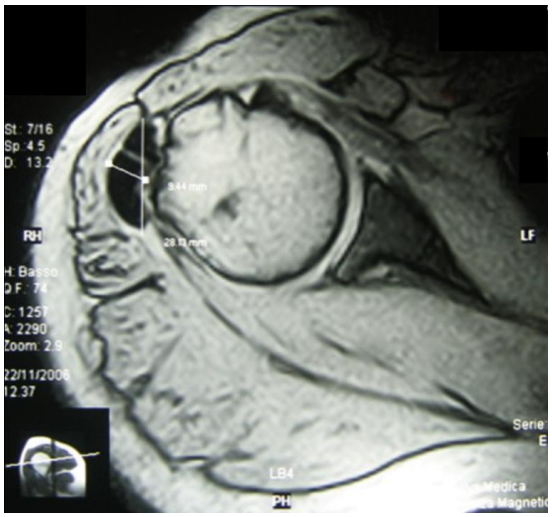

Figure 1: MRI in T1 of calcific tendinopathy of supraspinatus tendon > 2 cm.

Figure 2.

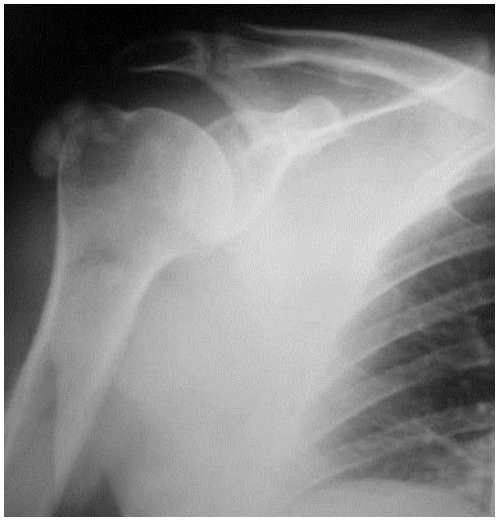

Figure 2: Preoperative radiograph of calcific tendinopathy of the supraspinatus tendon > 2 cm.

Figure 3

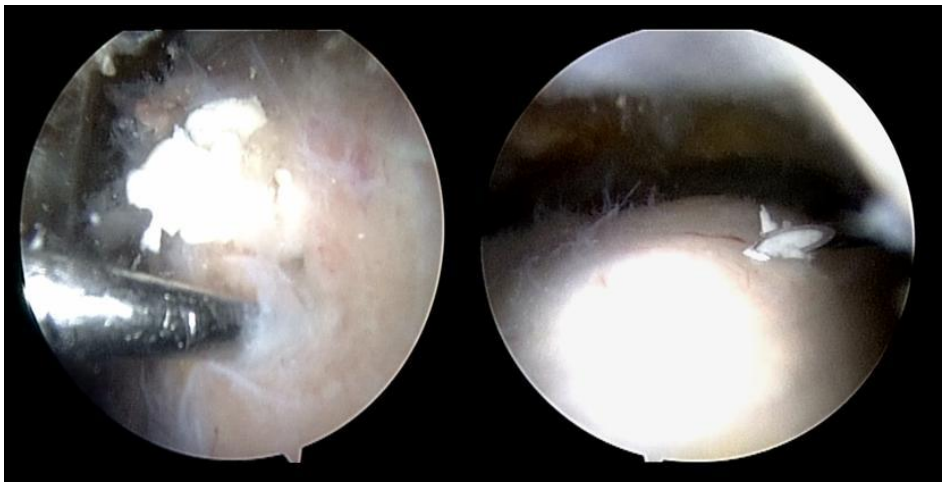

Figure 3: Arthroscopic treatment of calcific tendinopathy of the supraspinatus tendon > 2 cm: intraoperative imaging.

Figure 4

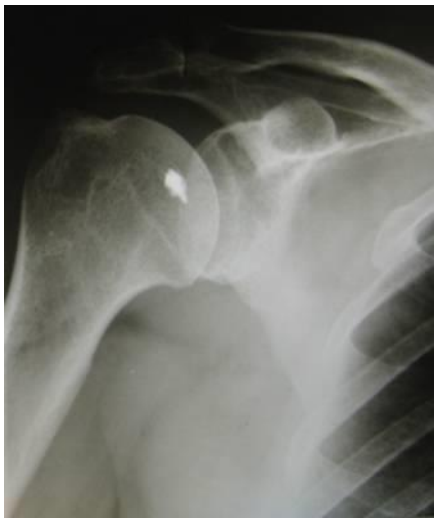

Figure 4: Post-operative radiograph of a calcific tendinopathy of the supraspinatus tendon > 2 cm, sutured with a metallic anchor.