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Case Report

REVISITING THE STATE-OF-THE-ART KNOWLEDGE OF SHOULDER CALCIFIC TENDINITIS PATHOGENESIS, DIAGNOSIS, AND TREATMENT: AN EVIDENCE-BASED REVIEW

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ABSTRACT

Shoulder calcific tendinitis is a common debilitating disorder characterised by the presence of either single or multiple calcium deposits in the rotator cuff tendons or the subacromial-subdeltoid bursa. Although this disease tends to subside spontaneously, a large percentage of patients still report shoulder pain and dysfunction, even after therapy. Several treatment options are available for shoulder calcific tendinitis, but clear therapeutic guidelines are still lacking and clinical outcomes are often controversial, likely due to lack of understanding of its pathophysiology. This evidence-based narrative review aims to revisit the base of the pathogenesis, diagnosis, and treatment of calcific tendinitis affecting the shoulder rotator cuff, specifically focusing on the most recent scientific findings.

KEYWORDS: *calcific tendinitis, shoulder, rotator cuff, diagnosis, therapeutic strategies*

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INTRODUCTION

Calcific tendinitis is a painful, self-limiting disorder most commonly observed in the shoulder girdle, and characterised by either single or multiple calcium deposits in the rotator cuff tendons or in the subacromial bursa (1).

Over the years, different terminology has been used to describe this disease. At first, the deposits in the subacromial bursa were described as the main radiological feature. Later, Codman (2) and Plenk (3) respectively identified the deposits inside the rotator cuff tendon and coined the term "calcifying tendinitis".

Epidemiology

Shoulder calcific tendinitis occurs in 2.7% to 42% of the population worldwide (1, 4-7). Deposits are bilateral in 10-20% of cases (1, 5, 8). Women are affected 60% more than men and it occurs more frequently in sedentary workers (9, 10). Calcific Tendinitis is typically seen in younger patients aged between 30-50 years (11), but it can rarely occur in the elderly as well (7, 12, 13). It is associated with metabolic disorders such as insulin-dependent diabetes (14), hyperlipidaemia, hypothyroidism, and disorders of estrogen metabolism (15). Biochemical features that play a role in the formation of calcium deposits include extracellular tendon matrix glycosylation observed in diabetic patients and genetic predisposition (14).

Among shoulder rotator cuff tendons, the supraspinatus is the most frequently affected (80% of the cases) (1, 3, 4, 16), while the infraspinatus and subscapularis are affected in 15% and 5% of the cases respectively, and the teres minor is only rarely affected (1, 4, 16). The right shoulder is the most commonly affected (16).

Although calcific tendinitis subsides spontaneously, in most cases, physical therapy and pain management, extracorporeal shock wave therapy, ultrasound-guided percutaneous lavage, orthobiologic therapy, and surgical debridement were demonstrated to relieve pain and restore shoulder function. Conservative treatment can accelerate recovery and healing; however, shoulder calcific tendinitis can be a recurring condition, which is a major clinical concern. In addition, despite treatment, pain and upper-arm disability are still a concern in many patients, reducing their quality of life.

This evidence-based narrative review aims to revisit the basis of the pathogenesis, diagnosis and treatment of calcific tendinitis affecting the shoulder rotator cuff, based on the most recent scientific literature. This will provide an update on the understanding of the pathogenesis of calcific tendinitis and the available therapeutic strategies.

Pathogenesis and natural history

Various authors have tried to explain the pathogenesis of calcium deposits; however, controversy still exists. Possible causes include degeneration due to overuse2, local tendon seat ischaemia (17), tenocytes necrosis due to apoptosis (18), and degenerative processes that involve necrotic changes in the tendon fibres that can progress into dystrophic calcification (19).

Analysing the anatomical and pathophysiological features of calcific tendinitis, literature reports the calcification within a viable and well vascularised rotator cuff tendon. It occurs within the structure of the rotator cuff, 1 to 2 cm proximal to its insertion.

Classically, the condition will end by spontaneous resolution, and it is uncommon to see other signs of degenerative changes (20). Discriminating between dystrophic calcification (calcification within a non-viable and poorly vascularized rotator cuff) and calcific tendinitis deposit (the deposition of calcium hydroxyapatite crystals within a pathologically healthy tendon (21) is of paramount importance. Unlike the calcification seen in degenerative tendinopathy, which is composed of a heterogenous mixture of calcium salts diffusely scattered throughout the tendon in areas of collagen degeneration or tear [add: 1a], CT calcification (hydroxyapatite crystals) presents as a focal deposit in the 'critical zone' (1-2 cm from the insertion of a tendon) (22), "*where there is thought to be high shear and stress forces that initiate the development of a focal calcific deposit between healthy collagen fibers*" (21). CT typically involves the formation of a single foci of calcium hydroxyapatite crystals embedded between grossly healthy fibrils of collagen. On the other hand, degenerative tendinopathy results in the breakdown of type I collagen and subsequent diffuse intratendinous calcification (23).

In light of the aforementioned consideration, the prevalent theory for the development of CT is that of 'failed cell-mediated healing'10, whereby repetitive microtrauma and excessive loading conditions trigger a non-physiological healing response and induce focal calcification formation. Previous authors described the progression of shoulder calcific tendinitis to follow distinct pathological stages correlated with disease presentation along with clinical features (22, 24). At first, the pre-calcific stage is characterised by the fibrocartilaginous metaplasia of tenocytes into chondrocytes inside the tendon, predisposition to an evolving situation. This stage is generally asymptomatic, and the patient does not realise

that calcification may develop. The following calcific stage is subdivided into three phases: formative, resting, and reabsorption.

In the formative phase, a chronic process resulting from transient hypoxia that is commonly associated with repeated microtrauma responsible for inducing metaplasia into chondrocytes, the deposits develop into bone foci that later coalesce, typically with a chalk-like appearance (22, 24).

Incorrect differentiation of stem cells (TDSCs: tendon-derived stem cells), into osteoblasts or chondrocytes, could be the basis of calcification and the fibrocartilaginous transformation of tendon tissue (25). Once the calcification has formed, the patient enters into the painless resting phase that may last for a varied length of time before the resorption process starts.

During the resorptive phase, the acute inflammatory reaction to the calcific deposits is mediated through macrophages and multinucleated giant cells migration in the tendon, which infiltrate and phagocytose the calcific deposits, and vascularised tissue develops at the calcification periphery (26). This results in rising intratendinous pressure, consequent mechanical secondary impingement due to tendon size increase, and the onset of symptomatology.

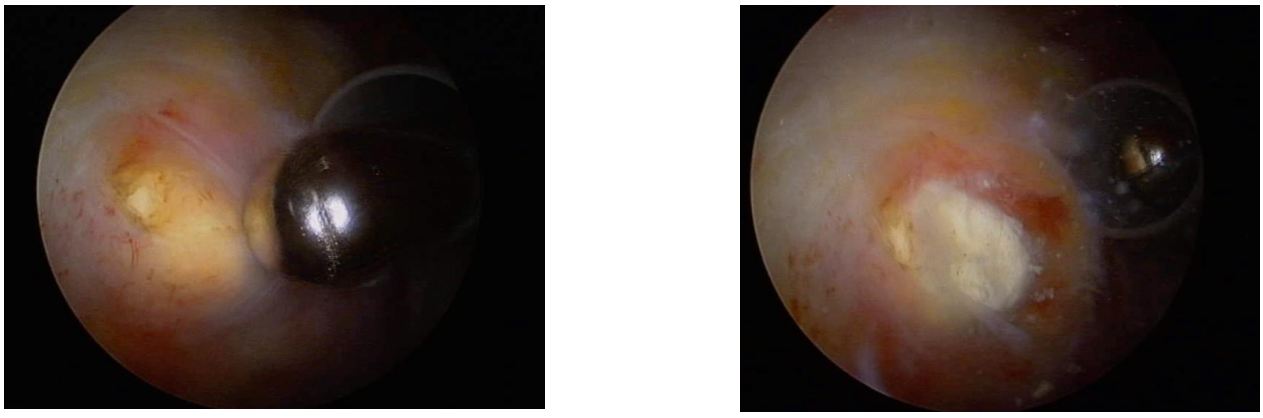
The calcification at this phase resembles the consistency of toothpaste and can leak into nearby bursae, bone, or muscle, causing severe pain. Patients complain of symptoms progressing from diffuse pain to focal impingement, and finally, severe localized pain prior to resolution.

The last post-calcific/reparative/healing phase consists of reabsorption of the deposit and remodelling of the previously occupied space. Thus, calcium is substituted by type-II collagen and subsequently replaced within 12 to 16 months by Type I collagen, resulting in tendon restoration of both normal collagen pattern and architecture, and leading to complete rotator cuff tendon healing (27, 28).

Clinical presentation and natural history

The clinical manifestation of CT is highly variable. It can be asymptomatic, discovered serendipitously by X-rays, or progress from diffuse pain to focal impingement and finally severe localised, acute, disabling pain, prior to resolution. Furthermore, a clinical picture involving concomitant stiffness giving rise to a frozen shoulder can also be seen. The unpredictable clinical presentation was demonstrated to depend on both disease stage (at any stage patients may not display any symptoms), as well as the anatomic location in the shoulder (6, 7).

For this reason, clinical correlation with radiographic imaging findings is critical to ensure an accurate diagnosis by discriminating between the symptoms arising from severe acute inflammatory response and mechanical long-lasting impingement due to large calcific deposits, responsible for associated loss of shoulder range of motion.



(A) *(B)*

Fig. 1. *mechanical long-lasting impingement due to large calcific deposit deposit (2 cm), responsible for associated loss of shoulder range of motion. Arthroscopic steps in a patient with chronic calcific in the supraspinatus tendon: Intraoperative view. After identying the deposit (a), calcium is progressively removed (b).*

Given that, the natural history of the disease can be divided in the three distinct clinical stages of acute, subacute, and chronic, despite the fact that symptomatology may vary significantly from patients who are completely asymptomatic to those presenting with acute, debilitating pain, which may or may not be associated with acute or gradual restriction of movements (29).

Clinical presentation, characterising the formative stage, consists of subacute, low-grade, general pain that may be more pronounced or noticeable at night or, with increased pressure in the area, provoked by shoulder movements, without localizable or specific findings (30).

Most patients progress into the resting stage after 3-6 months. However, remarkably, and inexplicably, the chronic formative phase may persist for months to years unless treated in about 10% of the patients (9, 15).

Symptoms become more mechanical in the resting phase, as stabilization of CT develops into a single calcified mass, causing secondary shoulder impingement and altering the intrinsic tendon's elasticity**.** Consequently, patients may complain of snapping, clicking, or catching sensations, with localized pain in the joint (24, 31).

Although the deposits could be asymptomatic in about 20% of cases without symptoms at previous stages, classically, the resorptive stage is the most painful (11, 30, 32).

The pain may present acutely, accompanied by severe muscle spasms. Inflammation in nearby structures (subacromial bursa and long head of the biceps) is triggered by the extrusion of calcium and perpetrated by increased vascular flow, thus causing complications such as adhesive capsulitis, rotator cuff tear, long-head biceps pathology, and osteolysis of the greater tuberosity (33).

Even when a resorptive stage arises due to flare-ups of chronic tendinopathy, patients tend to complain of localized pain, swelling, and erythema, associated with limited range of motion in their joints (33, 34).

During the transition from the resorptive to the last reparative stage, patients will experience diminishing signs and symptoms until normal tendon structure and joint mechanics are restored (27).

Conventional radiography

Conventional radiography, with standard joint-specific views, is the primary imaging modality used to visualize and localize calcific deposits, as well as characterize the phase of the disease.

Radiographs, "plain X-rays" in antero-posterior, outlet, and axillary view are reported to be viable to diagnose and follow-up CT, accessing the texture and morphology of deposits, identifying stages, and ruling out concomitant associated osseous abnormalities (29, 32).

Radiographic aspects of CT were the first used for classification by many authors for evaluating the deposits in terms of size and morphology, and for demonstrating that inter-observer variability is significantly high (35, 36-39).

Although there is no classification that perfectly matches the radiographic findings and clinical presentation, the morphological characteristics of the deposits correlated with the histologic stage could be described as follows: the resting phase is recognizable when observing well-circumscribed and dense deposits, while the formative phase is circumscribed with an inhomogeneous structure or poorly circumscribed with a homogeneous structure, and the resorptive phase is defined when calcium appears poorly circumscribed and is radiographically translucent (36).

Ultrasound

Ultrasound (US), also called sonography or diagnostic sonography, is a complementary diagnostic imaging modality of choice for CT that is extremely useful in the diagnosis and treatment of calcific tendinitis (36, 40). In fact, the use of high-resolution US has demonstrated superior ability to visualize CT at all stages and to guide therapeutic interventions (41).

Over the years, the role of US has turned from purely diagnostic to concretely operative, making sonography a therapeutic tool of paramount importance for carrying out percutaneous procedures (bursal lavage and tendon needling).

Ultrasonography is considered safe but highly operator-dependent, and in the hands of a skilful operator it can be used to easily identify the deposits' location, size and texture, and detect associated lesions. Furthermore, US is extremely useful not only for identifying the calcification, but also for staging the deposits, by means of correlation shadow cones, with the pathological state (42, 43). To go into further detail: CT sonographic features are characterized by hyperechoic focus within the fibular pattern of the healthy tendon, with posterior acoustic shadowing.

In the resting phase, the deposits appear hyperechoic and arc shaped, whereas in the resolving phase, they appear non arc shaped (fragmented/punctate, cystic, nodular). These appearances can also be correlated to the symptomatic and asymptomatic phases of the disease44. Some authors divided the deposits into three types: hyperechoic focus with a well-defined shadow, hyperechoic focus with a faint shadow, and hyperechoic focus with no shadow (36). Doppler examination during the reabsorption phase shows increased vascularity around the deposits due to phagocyte activity around the deposits (45).

Ultrasonographic findings associated with symptomatic CT include fragmentation, power Doppler signal, and distention or extrusion of calcium into surrounding bursal structures (36, 42). In addition, although ultrasound is most commonly utilized for CT surrounding the shoulder and distal extremities due to the superficial locations, it may still be

diagnostic for deeper structures. Newer scanning techniques, including compound scanning technology and elastography, hold promise for the evaluation of CT but need more investigation before routine use (46).

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a useful, but not essential, imaging tool for two reasons: first, because it does not give any additional information in most of the cases (47, 48), and second, because it is difficult to visualize calcium deposit with standard MRI due to the similar signal hypointensity of calcifications compared to normal tendon, thus leading to false-negatives and missed deposits or false-positives of normal hypointense, healthy tendons (48, 49). Nevertheless, MRI is useful to rule out other local joint and soft tissue pathology that may cause similar symptoms including tendon tears, osteoarthritis, and chondral or labral injury.

Areas of increased signal intensity can be found around the deposits in T2 images, signifying oedema around the deposits in the resorptive phase. This area of increased signal intensity can be misinterpreted as a RC lesion (49, 50). The accuracy of MRI in identifying calcific deposits is around 95%, but it is more useful in cases of chronic CT which could be associated with RC tears (Fig. 2), adhesive capsulitis, and osteolysis of the great tuberosity (33, 51).

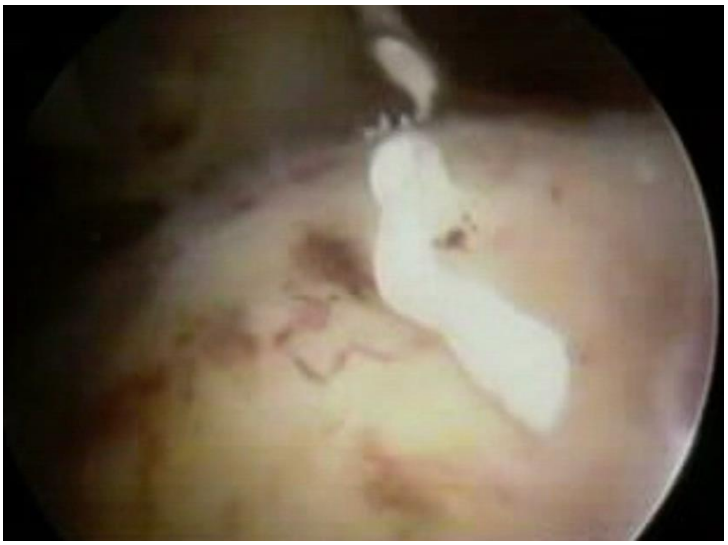


Fig. 2. *Calcific Tendinitis in the resorptive phase. Arthroscopic view: calcification at this phase resembles the consistency of toothpaste and can leak into nearby bursae, bone, or muscle, causing severe pain.*

Nevertheless, clinical correlation with imaging findings is critical to ensure an accurate diagnosis, especially when the CT is associated with other conditions, like shoulder stiffness, occurring in an acute stage of the disease that should be differentiated from both primary adhesive capsulitis and secondary stiffness following RC tears. Additionally, MRI has a high specificity for tendon and ligament tears as well as cartilaginous injuries that are important to identify and may be amenable to surgical repair or addressed intraoperatively. In chronic forms associated with TO, imaging assessment can allow for the differentiation from those occurring in association with dystrophic calcification and in tumours (52).

The employment of specialty sequences, including susceptibility weighted imaging, has allowed for the improved diagnostic ability of MR in comparison with conventional radiography, respectively 98% (sensitivity) and of 96% (specificity), for the identification of calcifications when compared with radiography, thus leading to better diagnostic performance than standard shoulder MRI protocols (53).

Conservative treatment

Considering the natural course of the calcific tendinitis, conservative therapy focused on symptomatic relief and shoulder functional improvement is the first line option of a stepwise algorithm including anti-inflammatory medications (NSAIDs administration), physical therapy, activity modification, UGN (Ultrasound Guided Needling), and ESWT (Extra Corporeal Shock Wave Therapy) (54).

Although literature reports little evidence regarding the individual efficacy of any particular treatment, treatment can be modulated to include the following, depending upon the presence of specific negative prognostic factors in the

early phase of the disease associated with high prevalence of "*failure of nonoperative therapy*" (persistence of symptomatic CT of the shoulder after a minimum of 6 months of treatment): bilateral calcific deposit, location close to the acromion, medial (subacromial) extension and large size of the calcific deposit (54).

Usually, the acute phase requires oral NSAIDs that are commonly prescribed due to their ability to provide pain relief through analgesia and a reduction in inflammation (55). Given no direct comparison studies, even topical NSAIDs, which have been demonstrated to result in lower systemic complications, are recommended. Appropriate physiotherapy can be utilized as a co-intervention to reduce pain and avoid shoulder stiffness, thus limiting NSAIDs administration and consequently reducing long-term gastrointestinal, renal, and cardiovascular side effects (55).

Physiotherapy, as reported, could be beneficial to preserve articular and tendon mobility, prevent gleno-humeral stiffness, and optimize joint mechanics, thereby decreasing dynamic tendon impingement (56, 57). Range-of-motion exercises and periscapular and rotator cuff strengthening performed in combination may restore the biomechanics of any tendon affected by CT, but there is currently not sufficient evidence to guide rehabilitation protocols (56, 58, 59).

Overall, many adjunctive conservative modalities been evaluated for the treatment of CT, such as osteopathic manipulative therapy and/or friction massage , therapeutic ultrasound, transcutaneous electrical nerve stimulation (TENS), and acetic acid iontophoresis (60-62). Although in most cases, conservative treatment is enough for resolution of symptoms, there is limited evidence to recommend one specific treatment over another (46, 63).

Minimally invasive treatment

Minimally invasive procedures include isolated bursal or peritendinous injections and ultrasound (US)-guided procedures (injections and barbotage or needling and lavage). US is currently accepted as guidance when performing shoulder musculoskeletal procedures (64).

As previously mentioned, calcium deposition may be extruded from the tendons cranially towards the sub-bursal space and subacromial bursa. Intrabursal penetration, causing acute microcrystalline bursitis during active resorption of calcification, does not allow the patient to perform therapeutic exercises due to excessive pain. In this sense, the use of steroid injections, despite being a debatable topic, have demonstrated to be effective in relieving pain due to subacromial impingement and bursitis, but not in stopping deposit reabsorption (65, 66).

For this reason, US-guided percutaneous aspiration of calcific tendinopathy (US-PICT) is superior to subacromial bursa injections in this setting, and when associated with US-guided barbotage (needling and lavage) of the calcific deposition, the two are the main therapeutic options in this phase (67).

In addition, a two-step procedure involving US-guided lavage of the intratendinous calcific deposit (first step to reduce intra-tendinous pressure and promote/accelerate the clearance of hydroxyapatite crystals from the rotator cuff tendons) followed by a corticosteroid injection of the subacromial bursa (second step to reduce the risk of post-procedural bursitis) would be considered the best approach for this phase of calcific tendinopathy (64).

Needling procedure effectiveness was first demonstrated using fluoroscopy (68) and in association with lavage and needling, nowadays a common intervention in clinical practice, while performed under local anaesthesia and without requiring hospitalisation (69). This procedure is more useful in treating fluid calcifications characterising the acute phase, as showed in published a study of 121 patients with a 2-year follow-up that reported satisfactory results after 3 months (70).

A recent systematic review on UGN in CT concluded that due to the low quality of evidence, the efficacy of UGN could not be firmly established and additional randomized trials are required (71).

Extra corporeal shock wave therapy

ESWT is an option for the management of CT that has been used for medical treatment since the 90s, although the exact underlying mechanism of the therapeutic effect is still debated.

Regarding the direct mechanical effect, ESWT induces calcium deposit fragmentation due to the increasing pressure inside the deposit itself, while regarding its molecular effect, it seems to be related to the phagocytosis of calcium deposits induced by a neo-vascularization inflammatory response and leukocyte chemotaxis (72). This method is based on the application of repetitive pulses over the affected shoulder, which ca be low-energy (below0.08 mJ/mm2), medium-energy (0.08-0.28 mJ/mm2) and high-energy shock waves (0.28-0.60 mJ/mm2 (73).

The shock waves can be generated through electrohydraulic, electromagnetic, or piezoelectric mechanisms and are applied tailoring the dose on the patient. It was seen that between one single dose of 0.3 mJ/mm2 and two doses of 0.2 mJ/mm2, the former dose was more effective (74), and a 0.20 mJ/mm2 dosage was found to be more effective than 0.10mJ/mm2 (75). Furthermore, literature reported a study in that was in favour of high dose therapy, though the follow-up was of only 3 months, and they did not find any significant differences in the size of deposits on X-rays (76). In a RCT

where the control group was given sham treatment, the results were better in the ESWT group. The researchers also suggested other forms of treatment to patients who did not respond to ESWT after 6 months (72). Krasny et al. (59) compared ESWT alone and ESWT combined with UGN, and found that the combined treatment was more effective in relieving symptoms and that less patients in the combined treatment group required surgery (77). Daecke et al. (78), published a long-term follow-up in patients managed with ESWT which showed that 20% of overall patients required surgery and 70% of patients were treated successfully and no long-term complications were seen. Lee et al. (61) did a systematic review to find out midterm effectiveness of ESWT but due to the variability of treatment and reliability of the available studies, they were not able to conclude a particular dosage of treatment. Kim et al. (63) did a comparative study between UGN and ESWT and found better radiological and clinical outcomes in the UGN group, although both the groups showed improvement from the initial findings. As reported by literature, association with needling procedure could lead to better clinical results compared with ESWT alone (79).

Surgical approach

Arthroscopy is regarded as the last remaining modality in chronic cases in which conservative or less invasive approaches have failed. Once calcium deposits are arthroscopically identified by observing the "calcific bulging sign" within tendon structure, calcium removal is carried on. Literature describes different techniques regarding the type of tendon incision and the instrumentation used to remove the calcium deposit (29).

Open surgery should be considered a further option, given the fact that arthroscopic removal of deposits has been shown to give similar results as open surgery with less morbidity of the deltoid. However, surgery requires hospitalization, general anaesthesia or sedation, and quite a long rehabilitation period after treatment (80).

Some concerns arise about calcification size, as correlated deposits larger than 1 cm measured by X-ray were less susceptible to treatment with PT, corticosteroid injection, and ultrasound-guided aspiration, and were 2.8 times more likely to require surgical intervention.

One of the great advantages of surgery is that, while removing the calcification, the surgeon may also perform other procedures, such as subacromial decompression and thorough cleaning of the joint. In addition, many debatable issues regarding surgical technique are discussed: repairing versus leaving the defect created, complete versus incomplete removal of the deposits, removal of deposits versus acromioplasty only.

Ark et al. (81), published a report of 23 patients in which they suggested that complete removal of the deposits is not essential, and they did not attempt to repair the defects created following the removal of deposits. Other researchers suggested a similar approach. Jerosch et al. concluded in their study that repair is not required following removal of deposits, but they insisted on complete removal of the deposits (82-84).

On the contrary, Porcellini et al. recommended complete removal of deposits followed by repair of the defect in the tendon using simple side to side sutures or suture anchors, depending upon the size of the residual defect (85). They argued that repair gives similar results without the fear of propagation of the tear and also helps in early rehabilitation of patients. Tillander et al. (86) compared the outcome of acromioplasty in 50 patients, 25 of which had CT and another 25 which had other causes of impingement syndrome. They did not find any significant difference between the constant scores of both groups at 2 years and recommended that the deposits should be left alone. Most of the authors recommended informing patients about delayed recovery post-surgery and were of the opinion that surgical treatment should be reserved for patients not responding to conservative treatment for more than 6 months.

Complications in the treatment of calcific tendinitis of the shoulder

Various complications associated with calcific tendinitis were described as additional complications, such as secondary adhesive capsulitis and rotator cuff tears, both of which could occurring during the primary disease or post-surgical intervention, as well as ossifying tendinitis, which is an extremely rare condition following surgical removal of the calcium deposits87. Osteolysis of the greater tuberosity has been described as an occurrence along with calcific tendinitis of the rotator cuff (33, 88) (Fig. 3).

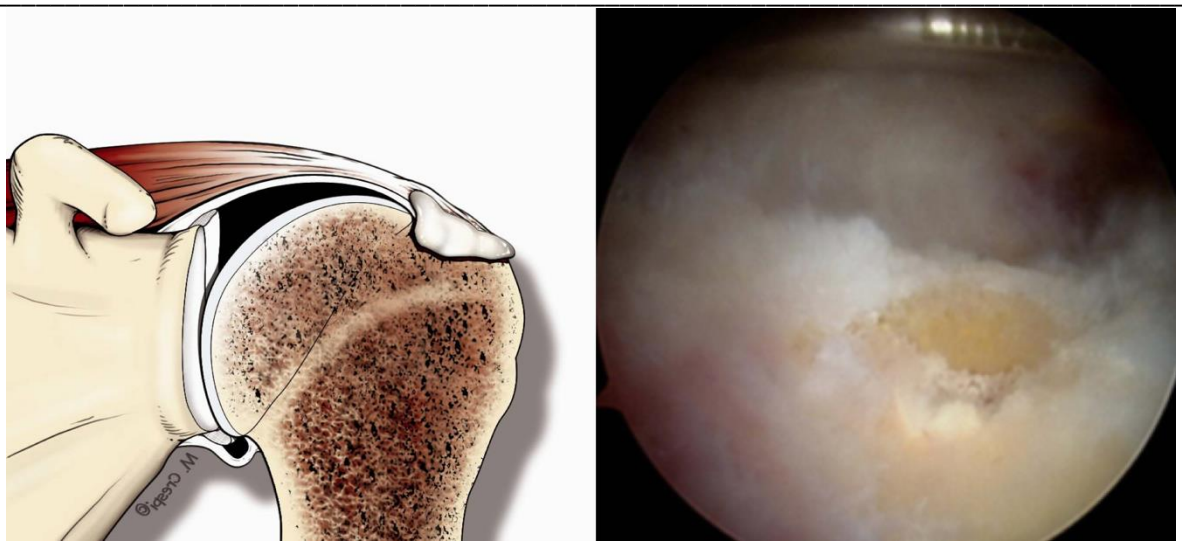


Fig. 3. *Arthroscopic view: greater tuberosity osteolysis***.**

CONCLUSIONS

CT of the RC is a controversial pathology with several treatment modalities, depending on the stage of the disease. Although it reabsorbs spontaneously in the majority of the cases, a subset of patients displays persistent pain in their shoulder, requiring conservative or operative management. In addition, some complications such as TO, adhesive capsulitis, or ossifying tendinitis (very rare) may give rise to prolonged pain that is resistant to common conservative therapies. UGN is indicated in the acute phase, but good results have also been found in patients with chronic calcific deposits. ESWT can be used reasonably successfully in chronic calcific cases, even in combination with UGN. Surgical treatment should be considered when conservative measures have failed or in cases of US or MRI evidence of RC tears.

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