Calcific tendinitis: Natural history and association with endocrine disorders

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A retrospective, observational cohort study of 102 consecutive patients (125 shoulders) with calcific tendinitis is presented. Of the patients, 73 (71.6%) were women and 29 (28.4%) were men. Compared with population prevalences, significant levels of endocrine disorders were found. We compared 66 patients (62 women [93.9%] and 4 men [6.1%]; mean age, 50.3 years) (81 shoulders) with associated endocrine disease with 36 patients (11 women [30.6%] and 25 men [69.4%]); mean age, 52.4 years) (44 shoulders) without endocrine disease. The endocrine cohort was significantly younger than the non-endocrine cohort when symptoms started (mean, 40.9 years and 46.9 years, respectively), had significantly longer natural histories (mean, 79.7 months compared with 47.1 months), and had a significantly higher proportion who underwent operative treatment (46.9% compared with 22.7%). Disorders of thyroid and estrogen metabolism may contribute to calcific tendinitis etiology. Classifying calcific tendinitis into type I (idiopathic) and type II (secondary or endocrine-related) aids prognosis and management. (J Shoulder Elbow Surg 2007; 16:169-173.)

In calcific tendinitis, the supraspinatus tendon is most frequently affected and is characterized by the multifocal accumulation of basic calcium phosphate crystals (hydroxyapatite) within the tendon. The natural history of calcific tendinitis is thought to be cyclic, occurring in 4 distinct stages, although the pathogenesis is still a matter of controversy.[1,7] It is known that tendon biology is influenced by gender and hormonal variations (particularly estrogens and thyroxine),[1,8] and it is hypothesized that endocrine and connective tissue disorders may be implicated in calcific tendinitis. The aim of this study was to investigate the natural history of the condition with an emphasis on the association with endocrine and connective tissue disorders.

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METHODS

Computerized hospital records were used to identify all patients diagnosed with calcific tendinitis between August 1996 and July 2001 at our institution. Plain radiographs of all cases were reviewed by the senior author. Cases in which radiographic evidence was inconclusive or that had clearly described dystrophic calcification associated with rotator cuff tears were excluded. With full ethical approval (Oxford Regional Ethics Committee Reference No. C01.171), all patients were interviewed in person by 1 researcher over a 3-month period (February to April 2003); each patient completed a questionnaire focusing on personal epidemiologic data, shoulder symptoms, treatment received, and medical history. Relevant medical problems were regarded as those for which the patient had undergone active treatment. Patients were asked whether they were satisfied with the outcome of their treatment and to document any residual shoulder deficit using a 5-category scale (where 1 indicates none and 5 indicates severe).

Significance testing was performed by use of the χ^2 correlation (with Yates correction for small sample size), as well as the 2-sample *t* test (corrected for small sample sizes).

RESULTS

Study cohort

Computerized hospital records identified 149 patients diagnosed with calcific tendinitis. Of these, 17 (11.4%) were excluded after radiographic review, 5 (3.3%) were lost to follow-up, and 25 (16.8%) declined to participate. The study cohort of 102 patients (125 shoulders) comprised 73 women (71.6%) and 29 men (28.4%) ($P = .0024$). Overall, the mean age at onset of symptoms was 43.5 years, with a significant difference in mean age at symptom onset between genders (41.6 years in women vs 48.3 years in men, $P = .0041$). Incidence was greatest between the fourth and sixth decades in both and absent in both the second and ninth decades. The age distribution for female and male participants is shown in

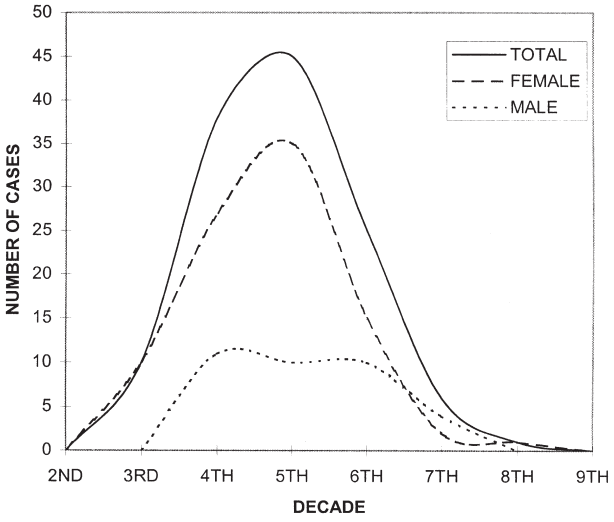

Figure 1 Distribution of ages of symptom onset and variation with gender.

Table I BMI, alcohol intake (as percent of RWI), and smoking habits by gender and for all cases

	Mean BMI (kg/m^2)	Mean alcohol intake (% of RWI)	Smoker (%)
Female	25.9	74.0	19.2
Male	27.0	72.4	17.2
Overall	26.2	73.5	18.6

RWI, Recommended weekly intake.

Figure 1. No significant difference in body mass index (BMI), alcohol consumption, or smoking was seen (Table I). Despite this, mean BMIs for both genders fell into the overweight category, alcohol consumption in both groups was significantly below recommended weekly alcohol intake guidelines (14 units in women and 21 units in men), and less than 1 in 5 patients in both genders were smokers. Calcific tendinitis was bilateral in 23 of 102 patients (22.6%). There was no gender difference in the number of bilateral cases: 17 of 73 women (23.3%) and 6 of 29 men (20.7%). Of the 79 patients (56 women, and 23 men) with unilateral calcific tendinitis, the dominant and nondominant arms of men and women were similarly involved (dominant in 48 [60.8%] and nondominant in 31 [39.2%]) (women, dominant in 36 [64.3%] and nondominant in 20 [35.7%]; men, dominant in 12 [52.2%] and nondominant in 11 [47.8%]).

All patients presented initially to a general practitioner at a mean of 17 months (range, 0.25-120 months) after the onset of shoulder symptoms. Of 102 patients, 48 (47.1%) took time off work (mean, 1.4 months, range, 0.25-4 months) because of their symptoms. Of 125 cases, 77 (61.6%) were treated nonoperatively. In 56 cases (72.7%), the patient was satisfied with the outcome of nonoperative treatment. In 48 cases (38.4%) nonoperative treatment failed, and arthroscopic subacromial decompression (ASD) with excision of the calcific deposit was performed. In 41 cases (85.4%), the patient was satisfied with the outcome of surgery.

Endocrine disease association

Of 102 patients in our study, 66 (64.7%) had previously been diagnosed with a specific endocrine disorder. A high prevalence of both autoimmune and hormone-related gynecologic diseases was found. Overall, 19 of 102 patients (18.6%) were undergoing treatment for a specific autoimmune disease (13 with hypothyroidism [9 women and 4 men], 4 with rheumatoid arthritis [all women], and 2 with type 1 diabetes [1 women and 1 man]). Compared with normal population estimates for the prevalence of these diseases (approximately 1.0% for each[20]), the prevalence of such diseases is significantly higher in our study ($P = .0026$ for hypothyroidism alone and $P = .0008$ for autoimmune disease overall). Of 73 female patients, 50 (68.5%) had undergone formal treatment for menstrual disorders. Within this group, 8 were diagnosed with endometriosis, 8 with ovarian cysts, and 2 with polycystic ovary syndrome, with 15 having undergone investigation/treatment for infertility or recurrent miscarriages. In addition, 21 patients (28.8%) had undergone laparoscopy and 23 (31.5%) hysterectomy. Up to 30.0% of the female population will at some point in their lifetime undergo treatment for menstrual disorders,[16] and 11.0% of all women will undergo hysterectomy as treatment for such conditions.[18] The prevalence of menstrual disorders and hysterectomy rates are significantly higher in our study than in the general population ($P < .0001$ and $P = .0016$, respectively).

Further analysis was performed comparing patients with associated endocrine disease and those without endocrine disease. The endocrine cohort comprised 66 patients (81 shoulders), 62 women (93.9%) and 4 men (6.1%), with a mean age of 50.3 years (range, 29.0-74.0 years). The non-endocrine cohort included 36 patients (44 shoulders), 11 women (30.6%) and 25 men (69.4%), with a mean age of 52.4 years (range, 35.0-73.0 years). The mean age of symptom onset in the endocrine cohort was 40.9 years (range, 20.0-72.0 years) compared with 46.9 years (range, 30.0-68.0 years) in the non-endocrine cohort ($P = .0026$). Incidence was greatest in the fourth and fifth decades for the endocrine cohort and in the fifth decade for the non-endocrine cohort (Figure 2). No significant differences were seen in the manner of symptom onset

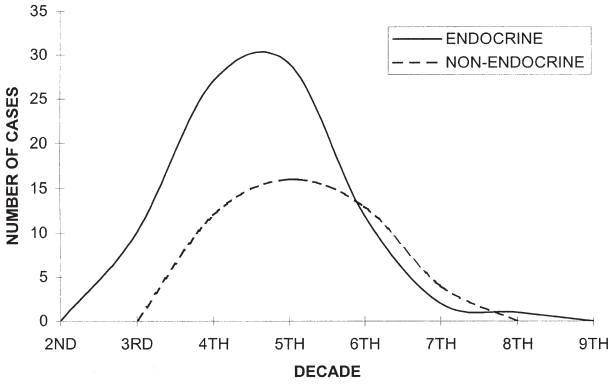

Figure 2 Distribution of ages of symptom onset for endocrine and non-endocrine cohorts.

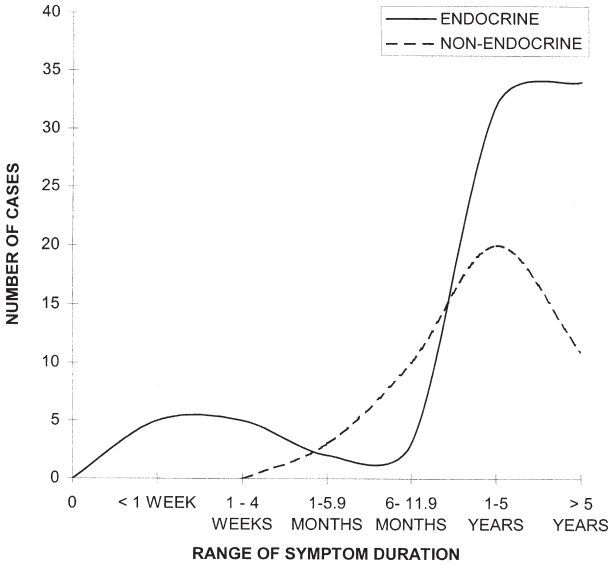

Figure 3 Distribution of range of symptom duration for endocrine and non-endocrine cohorts.

between the groups. In 15 of 81 shoulders (18.5%) in the endocrine cohort, symptom onset was acute (over 1-7 days), with the remainder describing a chronic picture of symptoms increasing over several months. For 7 of 44 shoulders (15.9%) in the non-endocrine cohort, the patients described an acute onset of symptoms. The overall duration of symptoms experienced by patients in the endocrine cohort was significantly longer (mean, 79.7 months, range, 0.25-420 months) than that the non-endocrine cohort (mean, 47.1 months, range, 0.25-180 months) ($P = .015$). Despite this, the endocrine cohort contained a small subgroup of patients (n = 5) in whom symptoms resolved within 1 week. The distribution of symptom duration for both groups is shown in Figure 3.

In 38 of 81 shoulders (46.9%) in the endocrine group, nonoperative treatment failed, and ASD with calcific deposit excision was performed. This was significantly higher than the non-endocrine cohort, in which 10 of 44 shoulders (22.7%) failed nonoperative treatment ($P = .014$). No significant differences were seen in levels of satisfaction or residual loss of shoulder function between endocrine and non-endocrine cohorts for both nonoperative and operative treatment. In addition, no significant differences were seen between cohorts for mean pain scores, time off work, BMI, alcohol consumption, smoking habits, the presence of calcific tendinitis bilaterally, or dominant arm involvement.

DISCUSSION

The reported prevalence of calcific tendinitis in the general population is highly variable, with estimates varying from 2.7% to 22%.[2,14] Such variations directly reflect the difference in study cohorts and radiographic techniques used. At our institution, 149 patients were diagnosed with calcific tendinitis over a 5-year period (with 102 participating in this study). These are patients who are symptomatic and in whom treatment in primary care has failed and, therefore, must represent a small subgroup of patients, given the reported population prevalence of this condition. Although previous studies have documented a female predisposition for calcific tendinitis,[2,3,6,12] with a peak prevalence in the fifth decade,[6,12] none has found a gender distribution as significant as that observed in this study. A variation in the age of onset between gender's has been suspected,[17] with Lippmann[12] reporting a mean age of onset in women and men of 47 years and 51 years, respectively. Our highly significant results support this suspicion. Calcific tendinitis is reportedly more common in the right shoulder,[17] although this does not necessarily reflect arm dominance. No relation with arm dominance was noted in our study, although 22.6% of patients were affected bilaterally (compared with 10%-17% in previous reports[6,17]). In addition, we found both men and women in our cohort to be overweight (in terms of BMI), with low levels of alcohol intake and smoking.

Unlike the widely reported self-limiting[15] and transient[9] nature of the condition, many patients in this study had protracted natural histories, almost half of which resulted in time off work. Codman[5] identified patients with both very short and protracted natural histories, hypothesizing that acute and chronic forms of the condition were, in fact, different diseases. In comparison, Uhthoff and Loehr[17] proposed a cyclic, 4-phase model for the condition's natural history, with variations in length of natural history explained by differing rates of progress through this cycle. Although no evidence exists to support Codman's hypothesis, it can be inferred that, if Uhthoff and Loehr's

model is correct, the presence of associated endocrine disease may slow or even arrest progression through its cyclic natural history, although the underlying mechanism for this is unknown.

Some authors have previously reported disease associations with calcific tendinitis.[17] Conditions such as carpal tunnel syndrome can be classified as idiopathic or secondary, with many well-documented conditions and disease associations being recognized (eg, pregnancy and hypothyroidism). In secondary cases, symptoms are known to improve rapidly with the resolution or treatment of the associated condition or disease.[11] We propose that calcific tendinitis should also be classified as idiopathic, type I, or secondary, type II. Given the prevalence of endocrine disease found in our study cohort, we believe that these may have an important role in the etiology and pathogenesis of calcific tendinitis, although the mechanism of this effect is unknown. We have found a highly significant prevalence of these diseases in our study. Thyroxine is important for both collagen synthesis and matrix metabolism. Hypothyroidism causes an accumulation of glycosaminoglycans in the extracellular matrix, which may, in turn, predispose to tendon calcification. Tendinitis has been reported as the presenting complaint in cases of hypothyroidism,[10] symptomatic relief being obtained by treatment of the primary thyroid deficiency. Estrogens are known to have wide-ranging effects on connective tissue metabolism. Women are known to have increased joint laxity, which is directly affected by levels of circulating estrogens. This may account for the high prevalence of joint hypermobility seen in women compared with men (as much as 5:1 in some studies).[4] Women have an increased incidence of anterior cruciate ligament (ACL) injuries in comparison to men (estrogen receptors having been identified in the ACL matrix[13]), and these occur most frequently in midcycle (ovulatory phase).[19] Coadministration of the oral contraceptive pill has been shown to protect against this cyclic predisposition. Six women in our study stated directly that their symptoms were always worse around midcycle. It remains to be determined whether tendon function and mechanical properties are also influenced in a similar way because, by use of a rabbit model, estrogen receptor expression has been identified in the Achilles, patellar, flexor digitorum longus, and extensor digitorum tendons.[8] The oldest woman in our cohort (75 years) was undergoing concurrent treatment for breast cancer, taking tamoxifen, a partial estrogen receptor antagonist, as adjuvant therapy. Few studies have investigated the biomechanical properties of male and female tendons. Goldstein et al,[7] reported that numerous mechanical properties of the flexor digitorum profundus were different; females tendons were found to be significantly stiffer with uniaxial tension than those of men. At the molecular level, it is well-known that there are gender differences regarding the induction and elaboration of inflammatory responses. The release of proinflammatory neurotransmitters, such as substance P and calcitonin gene-related peptide, can result in the release of biologic mediators from tissue mast cells (macrophages), resulting in neurogenic inflammation. This process, in addition to the increased production of matrix metalloproteinases, is directly influenced by female sex hormones. Considering these various mechanisms, it is possible that autoimmune disease and disorders of estrogen metabolism may contribute to the etiology and pathogenesis of calcific tendinitis. These effects may be intrinsic, at a structural and biochemical level, but a cyclical increase in shoulder joint laxity may provide an extrinsic contribution.

In conclusion, calcific tendinitis is a poorly understood condition in which symptoms can be protracted, resulting in time off work and impaired quality of life. Despite this, the majority of patients respond well to treatment, whether nonoperative or operative. We have identified significant levels of endocrine disease among our study population. Patients with associated endocrine disease have symptoms develop at a younger age, have a significantly more protracted natural history, and more frequently undergo surgical treatment than patients with no associated endocrine disease. It is possible that these diseases are linked to the etiology and pathogenesis of calcific tendinitis, and the condition should be regarded as either idiopathic or secondary.

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