Commentary & Perspective

Uncovering the Mystery of Idiopathic Adhesive Capsulitis

Commentary on an article by Hyung Bin Park, MD, PhD, et al.: "Association Between High-Sensitivity C-Reactive Protein and Idiopathic Adhesive Capsulitis"

Michael Khazzam, MD

Adhesive capsulitis was first described in 1872 by Duplay et al.[1] and was further defined by Codman[2] in 1934 as shoulder pain with loss of both active and passive range of motion in the setting of normal radiographs[3]. Since that time, the etiology behind idiopathic adhesive capsulitis has remained unknown. The lengthy natural history, phases (inflammatory or freezing, frozen, thawing), and risk factors for development have been well defined clinically[4-6]. Risk factors include diabetes, hypothyroidism, dyslipidemia, high blood pressure, female sex, and age of 40 to 60 years. Currently, we still do not completely understand why this inflammatory process occurs or what specific pathophysiologic factors allow for adhesive capsulitis to be a self-limiting condition.

In this present retrospective, Level-III, case-control study, Park et al. investigate elevated serum high-sensitivity C-reactive protein (CRP) as a marker for idiopathic adhesive capsulitis. The authors investigated 202 patients diagnosed with idiopathic adhesive capsulitis and 606 age and sex-matched controls. Blood sampling assessed high-sensitivity CRP (levels classified as either >1.0 mg/L or ≤1.0 mg/L), glycosylated hemoglobin A1c (HbA1c), fasting glucose, hypercholesterolemia, hypertriglyceridemia, inflammatory lipoproteins (hyper-low-density lipoproteinemia, hypo-high-density lipoproteinemia, hyper-non-high-density lipoproteinemia), triglyceride/high-density lipoprotein (TG/HDL) ratio >3.5, thyroid-stimulating hormone (TSH), diabetes, hyperthyroidism, hypothyroidism, and body mass index. Univariate and multivariable regression analysis found that body mass index, diabetes, fasting glucose level, HbA1c, dyslipidemia, TG/HDL >3.5, TSH, and high-sensitivity CRP >1.0 mg/L were associated with idiopathic adhesive capsulitis. Serum high-sensitivity CRP >1.0 mg/L was also significantly associated with diabetes, fasting glucose level, HbA1c, hypertriglyceridemia, hypo-high-density lipoproteinemia, and TG/HDL >3.5 in subjects with adhesive capsulitis. These findings indicate that there is an association with medical comorbidities and systemic inflammation as demonstrated by high-sensitivity CRP. Although these results further strengthen the associations of diabetes, dyslipidemia, and thyroid dysfunction with adhesive capsulitis, they still do not provide information that can be used to guide treatment or to predict symptom duration.

It may be that medical comorbidities have an additive inflammatory effect, as was found in a study by Park et al.[4] demonstrating that hyper-low-density lipoproteinemia and/or hyper-non-high-density lipoproteinemia in patients with diabetes were associated with adhesive capsulitis. Chan et al.[5] found a dose-dependent relationship of adhesive capsulitis and cumulative HbA1c level. The authors found that, for each unit increase over time of HbA1c level >7%, there was a 2.77% increased risk of development of adhesive capsulitis.

The pathophysiology regarding why the glenohumeral joint stiffens involves an inflammatory capsular reaction, associated synovitis with progression to fibrotic contracture, and hyperplasia or capsular thickening. Capsular tissue characteristics in the setting of adhesive capsulitis include leukocyte and myeloid infiltration, fibroblast accumulation, and increased vascularity. Andronic et al.[3] performed a systematic review to better understand the pathophysiology on a molecular level. Studies examined capsule and blood samples and found increased expression of various inflammatory cytokines including cyclooxygenase, tumor necrosis factor, and interleukins, and decreased matrix metalloproteinase (MMP). Cohen et al.[7] examined which genetic factors contributed to the risk of idiopathic adhesive capsulitis. Female carriers of the C allele of MMP-13 and G/G allele of MMP-9 had an increased risk of adhesive capsulitis (odds ratio [OR], 1.64 [95% confidence interval (CI), 1.20 to 2.26]; p = 0.002). Additionally, female carriers of the G allele of MMP-9 had an increased risk (OR, 1.51 [95% CI, 0.97 to 2.33]; p = 0.05). In contrast, male carriers of the C allele of TGFB1 (the gene for transforming growth factor [TGF]-β1) had a reduced risk (OR, 0.47 [95% CI, 0.23 to 0.96]; p = 0.04), and those who were carriers of the GG genotype of TGFBR1 (for TGF-β receptor 1) had an increased risk (OR, 4.11 [95% CI, 1.17 to 14.38]; p = 0.027). TGFB1 plays a role in the fibrotic and inflammatory process of the capsule tissue in adhesive capsulitis. TGFB1 regulates extracellular matrix (ECM) proteins including collagens, fibronectin-1, and tenascin, and the increased expression of these markers contributes to capsule inflammation and fibrosis. TGFBR1 gene upregulation has been found to be dependent on symptom duration[8].

Cho et al.[9] examined the role of MMP-2 and MMP-9 expression in the joint capsule using measurements made during shoulder arthroscopy. The overexpression of MMP-2 and MMP-9 in the joint capsule was associated with advanced adhesive capsulitis. MMP-2 and MMP-9 expression is controlled by platelet-derived growth factor, tumor necrosis factor-α, interleukin (IL)-1, and IL-6, which are all pro-inflammatory molecules. Based on the timing of expression, the authors hypothesized that the expression of both MMP-9 and MMP-2 may be useful to predict the stage of adhesive capsulitis.

The most important question that comes from this information is how to use these results in a clinical practice to counsel patients being treated for idiopathic adhesive capsulitis. Ideally, the results of this work can be extrapolated to future work that will allow for a definitive method to predict the expected duration for complete resolution of symptoms and the severity. Even more useful would be markers to predict which patients will most likely have a prolonged clinical course, as more aggressive intervention such as a surgical procedure may be offered earlier in the disease process. These factors will save patients from lengthy morbidity associated with adhesive capsulitis as well as the frustration that commonly occurs from the loss of shoulder function.

Michael Khazzam, MD

Shoulder Service, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center Dallas, Dallas, Texas

Email address: drkhazzam@yahoo.com

ORCID iD for M. Khazzam: 0000-0002-5093-0295

Disclosure: The author indicated that no external funding was received for any aspect of this work. On the **Disclosure of Potential Conflicts of Interest** form, *which is provided with the online version of the article*, the author checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (http://links.lww.com/JBJS/F743).

References

1. Duplay E. De la périarthrite scapulohumérale et des raideurs de l'épaule qui en sont la conséquence. Arch Gen Med. 1872;20:513-42.

2. Codman EA. The shoulder: rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa. Boston: T. Todd; 1934.

3. Andronic O, Ernstbrunner L, Jüngel A, Wieser K, Bouaicha S. Biomarkers associated with idiopathic frozen shoulder: a systematic review. Connect Tissue Res. 2019 Aug 7: 1-8. Epub 2019 Aug 7.

4. Park HB, Gwark JY, Jung J. What serum lipid abnormalities are associated with adhesive capsulitis accompanied by diabetes? Clin Orthop Relat Res. 2018 Nov;476(11): 2231-7.

5. Chan JH, Ho BS, Alvi HM, Saltzman MD, Marra G. The relationship between the incidence of adhesive capsulitis and hemoglobin A_{1c}. J Shoulder Elbow Surg. 2017 Oct; 26(10):1834-7. Epub 2017 May 8.

6. Hand GC, Athanasou NA, Matthews T, Carr AJ. The pathology of frozen shoulder. J Bone Joint Surg Br. 2007 Jul;89(7):928-32.

7. Cohen C, Leal MF, Loyola LC, Santos SEB, Ribeiro-Dos-Santos AKC, Belangero PS, Figueiredo EA, Wajnsztejn A, de Oliveira AM, Smith MC, Andreoli CV, de Castro Pochini A, Cohen M, Ejnisman B, Faloppa F. Genetic variants involved in extracellular matrix homeostasis play a role in the susceptibility to frozen shoulder: a case-control study. J Orthop Res. 2019 Apr;37(4):948-56. Epub 2019 Mar 20.

8. Rodeo SA, Hannafin JA, Tom J, Warren RF, Wickiewicz TL. Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. J Orthop Res. 1997 May;15(3):427-36.

9. Cho CH, Lho YM, Hwang I, Kim DH. Role of matrix metalloproteinases 2 and 9 in the development of frozen shoulder: human data and experimental analysis in a rat contracture model. J Shoulder Elbow Surg. 2019 Jul;28(7):1265-72. Epub 2019 Mar 4.