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# Adhesive capsulitis: An age related symptom of metabolic syndrome and chronic low-grade inflammation? ☆

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ABSTRACT

Adhesive capsulitis (AC) is very poorly understood, particularly it's underlying etiology. Obesity and metabolic syndrome, which are strongly associated with chronic low grade inflammation, are becoming increasingly understood to underlie a raft of morbid states including upper limb pain syndromes, diabetes (DM), cardiovascular disease (CVD), cancer and central nervous system dysfunction and degeneration. Notwithstanding age, two of the strongest established risk factors for AC are DM and CVD. The hypothesis argues that similar to DM and CVD, the inflammation and capsular fibrosis seen in AC is precipitated by metabolic syndrome and chronic low grade inflammation. These pathophysiological mechanisms are highly likely to be perpetuated by upregulation of pro-inflammatory cytokine production, sympathetic dominance of autonomic balance, and neuro-immune activation. The hypothesis predicts and describes how these processes may etiologically underpin and induce each sub-classification of AC. An improved understanding of the etiology of AC may lead to more accurate diagnosis, improved management, treatment outcomes, and reduce or prevent pain, disability and suffering associated with the disease. The paper follows on with a discussion of similarities between the pathophysiology of AC to general systemic inflammatory control mechanisms whereby connective tissue (CT) fibrosis is induced as a storage depot for leukocytes and chronic inflammatory cells. The potential role of hyaluronic acid (HA), the primary component of the extracellular matrix (ECM) and CT, in the pathophysiology of AC is also discussed with potential treatment implications. Lastly, a biochemical link between physical and mental health through the ECM is described and the concept of a periventricular-limbic central driver of CT dysfunction is introduced.

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## Introduction and background

### *Definition and classification*

Adhesive capsulitis (AC), also commonly known as frozen shoulder, is an inflammatory and fibrotic disorder predominantly of the coracohumeral ligament (CHL) and rotator interval [1,2]. AC leads to considerable pain, restricted active and passive range of motion, with a protracted morbid state [1–3]. A review and consensus definition by the membership of the American Shoulder and Elbow Surgeons, in 2011, further established a sub-classification into primary and secondary AC (Table 1) [2]. Primary AC is considered idiopathic, whereas secondary AC is classified into one of three categories depending on its association with either another intrinsic shoulder pathology, an extrinsic pathology outside the shoulder, or systemic illness (Table 1) [2]. The overwhelming consensus regarding AC is that it is very poorly understood, particularly the underlying etiology [1–4]. AC has even previously been labelled as the 'enigma' of the shoulder [5].

### *Etiology, pathophysiology, epidemiology*

A consistently reported finding in AC research is that it is age related [1–4]. It is rarely seen before age 40, and apparently it is referred to as fifty year old shoulder in Japan and China [3,6]. Due to the unknown etiology underlying the reported pathophysiological findings in AC, it's strongest associated risk factors have seemingly eventuated to be considered separate entities (Table 1) [1–4]. Recent reviews have suggested the term 'adhesive capsulitis' should be abandoned as no articular adhesions are associated with the pathophysiology [3,6]. However, capsular adhesions, particularly of the extracellular matrix (ECM), are probably fundamental to the capsular fibrosis evident in AC [1,3,7–10]. AC is purported to progress through three or four stages which are probably best described as a painful inflammatory stage without capsular restric-

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**Table 1**
Classification of adhesive capsulitis (AC) [2].

| Primary AC | Secondary AC | Secondary AC | Secondary AC |
|---|---|---|---|
| Idiopathic | Systemic<br>Diabetes cardiovascular disease, other | Extrinsic<br>Proximal or distal surgery, trauma, other | Intrinsic<br>Rotator cuff tendinopathy, Calcific tendinitis, other |

tion, followed by a freezing, frozen and thawing stages [1,3,11,12]. The reported lifetime incidence of AC in the general population is 2–5%, with a large cross sectional study in the UK reporting a prevalence of 8–10% [1,3,13]. AC is considered self-limiting, historically thought to fully resolve within 1–2 years, however, more recent reports of average duration to resolution of 30 months is now considered as sub-optimal and is further confounded by reports of longer term symptoms and disability in many cases [3,6,14,15]. Systemic AC, particularly in DM, is associated with a prolonged disease course [1–4].

*Diagnosis*

AC has been reported as often being over diagnosed or misdiagnosed [4,16]. Diagnostic criteria are varied, however, significant loss of passive shoulder range of motion, particularly external rotation and elevation, appear to be more consistently reported and utilised in research [1–4,13,17,18]. The need to reliably identify the condition in its early inflammatory stage is becoming increasingly apparent as by the time the condition is obvious to the clinician or researcher, fibrosis has set in and the disease course is protracted, even with implementation of what may be considered successful management [11,12,19,20].

*Obesity, metabolic syndrome, oxidative stress*

The medical profession is becoming increasingly aware that modern society is facing an obesity epidemic, strongly associated with increased rates of morbidity and mortality [21–23]. The accepted primary link between obesity and its associated morbidities, such as diabetes (DM), cardiovascular disease (CVD), neurodegeneration and cancer, amongst others, is the metabolic syndrome [24,25]. Metabolic syndrome is precipitated by endothelial dysfunction due to hyperinsulinemia, pro-inflammatory cytokine upregulation and oxidative stress which results in excessive production of reactive oxygen species (ROS), advanced glycation end products (AGP) and a chronic low grade inflammatory state [26–30]. These processes also display strong correlations with age [26–33]. Given strong associations between AC, age, DM and CVD, the hypothesis postulates that they may share a common underlying etiology.

## The hypothesis

*Metabolic syndrome, chronic low grade inflammation and AC*

The hallmarks of metabolic syndrome are excessive abdominal adipose tissue, elevated triglycerides, blood pressure, fasting blood glucose, and decreased high density cholesterol levels [24,32]. Given the strong associations of AC with age, DM and CVD, the hypothesis predicts that metabolic syndrome and chronic low grade inflammation may be the shared underlying etiology. Evidence of elevated blood glucose, lipids and cholesterol have been demonstrated in AC [34,35]. In an otherwise previously healthy sample of 56 cases with early stage primary AC, Gumina and colleagues found 23% were hyperglycaemic, 68% had high total cholesterol, 64% had elevated low density lipoprotein and 43% displayed elevated triglycerides [35]. Austin and co-workers found a strong association between hyperglycaemia and AC and a possible association between hypertension and AC, however, this study suffered from a number of limitations which are discussed below [36]. Furthermore, visceral fat has been demonstrated to be associated with upper limb pain syndromes, of which AC constitutes a significant portion [13,37]. More studies are required which assess all parameters of metabolic syndrome simultaneously, however, the above reasoning and data does suggest that metabolic syndrome, particularly in the context of secondary systemic AC, may be a primary underlying etiological factor [2]. Interestingly, in metabolically sub-clinical individuals who are actually pre-diabetic, such as those reported in the study by Gumina and colleagues, these cases could potentially be considered secondary systemic AC rather than primary idiopathic AC, further supporting the hypothesis [2,35].

*Chronic low grade inflammation, autonomic dysregulation and AC*

Recent research strongly suggests many chronic disease processes, including upper limb pain syndromes, diabetes, cardiovascular disease, depression, and neurodegeneration, are associated with a dysfunction of autonomic nervous system balance [37–42]. Although causality has not been established, relative autonomic sympathetic dominance, usually indexed noninvasively as decreased heart rate variability (HRV), is thought to induce, or perpetuate, endothelial dysfunction and chronic low grade inflammation, largely through adrenergic activation of nuclear factor kappa beta (NF-κβ) [28,38–45]. Chronic low grade inflammation is distinct from acute inflammation resulting from injury or infection in that it is not localised, is of lower magnitude and longer duration, with no obvious stimulus [45]. Histological analysis of tissue biopsies taken from patients with adhesive capsulitis by Hand and colleagues are consistent with a chronic inflammatory state [8,9,46]. Furthermore, chronic low-grade inflammation is strongly associated with upregulation of pro-inflammatory cytokine production, sympathetic dominance of autonomic balance, and neuro-immune activation [28,38–45,47]. Evidence of increased presence of chronic inflammatory, cytokine and immune cells in AC, unspecific to the primary or secondary forms of the disease, is also consistent with the hypothesis [8,9,46,48].

*Shoulder functional design, modern lifestyle, altered ECM adhesion dynamics*

The human shoulder evolved for high speed projectile throwing which is largely dependent on elastic energy storage and generation of maximal shoulder external rotation range of motion [49]. Modern trends of sedentary lifestyle with a relative decrease in overhead utilisation of the upper limb very likely leads to parts of the shoulder capsule-ligamentous complex not being exercised or stretched sufficiently, compared to its evolutionary design [7,10,23,49–52]. Subsequently, parts of the shoulder capsule-ligamentous complex are probably subjected to accentuation of age related oxidative stress and pro-inflammatory cytokine production which leads to increased production of ROS, AGP and probable sub-clinical deleterious alterations in connective tissue (CT) and extracellular matrix (ECM) adhesion dynamics [7–10,29,50,53]. This is supported by data which demonstrates range of motion restriction in the asymptomatic contralateral arm of subjects with AC with long term follow up [14]. Therefore injury proximal or distal to the shoulder could induce a segmental and or systemic pro-inflammatory cytokine, sympathetic and neuro-immune response and forms a plausible mechanism by which secondary extrinsic AC may develop [2,7–10,38,39,41,45,47,48,53,54].

This is consistent with research on animal models whereby synovial capsule pro-inflammatory and fibrotic markers increase with the extent of immobilisation and are accentuated by surgery and trauma [8,9,55–59].

*Coracohumeral ligament anatomy, synovitis, AC and psychosocial stress*

The anatomical arrangement of the CHL in bifurcating cephalocaudally to the anterior portion of the supraspinatus tendon as it courses laterally from the coracoid process makes this structure particularly vulnerable to both internal and external impingement [60,61]. Given the ubiquity of impingement in various shoulder dysfunctions, any resulting local and segmental pro-inflammatory cytokine, sympathetic or neuro-immune upregulation, is a plausible mechanism by which the onset of secondary intrinsic AC could be initiated [1–3,8,9,39,60–64]. This is further supported by data which demonstrates quite similar increases in cytokine localisation patterns in synovial and capsular tissue biopsies of patients with and without adhesive capsulitis undergoing shoulder arthroscopy [48]. Moreover, the accepted AC pathophysiology of initial synovial inflammation and hyperplasia which progresses to chronic inflammation and capsular fibrosis is consistent with current understanding of general human inflammatory control mechanisms and studies of magnetic resonance imaging correlated to clinical staging of AC [1,8,9,46,48,65]. Interestingly, in the absence of other pathology with imaging and an insidious onset, sub-acromial impingement related pain with subsequent local and segmental pro-inflammatory cytokine and neuro-immune upregulation provides a plausible biomechanical rationale for potentiating the onset of primary adhesive capsulitis [1–3,8,9,46,48,60–62,66–68]. Moreover, psychosocial stress has been demonstrated to induce endothelial dysfunction and inflammation also through adrenergic mediated upregulation of the NF-κβ pathway [39,41,43–45,47,54]. Thus an increase in psychosocial stress leading to pro-inflammatory cytokine, sympathetic and neuro-immune upregulation, is also a plausible mechanism by which chronic low grade inflammation and/or subclinical capsular ECM alterations could be accentuated potentiating the onset and clinical symptoms of AC. In the absence of other clinical pathology, this is would also be considered primary adhesive capsulitis [2].

## Against the hypothesis

Although the study by Austin and co-workers reported a strong association between hyperglycaemia and AC and a possible association between hypertension and AC, overall the authors concluded that there was an unclear relationship between metabolic syndrome and AC [36]. However, results of this study should be viewed with caution as it was a retrospective medical record case control series of 150 subjects presenting to a sports medicine clinic utilising Body Mass Index and medication as diagnostic criteria for metabolic syndrome [24,36]. However, this study is important as it does raise the issue confounding by prescription of medications as these are likely to attenuate the symptoms of metabolic syndrome but have a currently unknown effect on heart rate variability [35,36,38,42].

## Implications of the hypothesis

*Research and prevention*

The hypothesis predicts that age matched populations over 40 years with obesity, metabolic syndrome and decreased HRV will show significantly greater incidence of AC compared to healthy controls without obesity and metabolic syndrome who participate in physical activity to recommended standards and have normal HRV. However, given the normally high physiological mobility of the shoulder, as discussed above, this effect may be more pronounced in samples that include regular dedicated stretching of the shoulder, such as yoga, as part of their regular physical activity regime. If substantiated this could strengthen the preventative efficacy of current physical activity guidelines [69–71]. In turn, this may prevent much pain, suffering and disability and provide financial savings to individuals and health systems.

*Diagnosis and management implications*

The hypothesis posits metabolic syndrome and chronic low grade inflammation as common etiological mechanisms which underlie pathophysiological changes of the classifications of AC. If the hypothesis is substantiated it may improve understanding of other aspects of the condition such as diagnostics and epidemiology which could result in improved management strategies and treatment outcomes. There is an obvious need to develop valid diagnostic criteria to detect the condition early in the inflammatory stage before obvious clinical fibrosis has set in [11,12,20]. The external rotation test and coracoid palpation test have been previously independently reported and are consistent with the functional anatomy of the CHL and rotator interval [11,12,18,19,72]. The hypothesis predicts that risk ratios for developing AC rise steeply between the ages of 40 and 50. Subsequently, the hypothesis predicts that combining age over 50, positive external rotation test and coracoid palpation test in a diagnostic test cluster will demonstrate acceptable validity for diagnosing early stage AC. If the hypothesis predictions are substantiated, improved early diagnosis may direct management towards improved outcomes such as prevention of significant loss of passive range of motion, decreased disability and shortened disease duration. Furthermore, improved diagnosis may clarify some epidemiological issues such as potential over diagnosis in those below 50 years and misdiagnosis in those above 50 years [4,16]. This is consistent with evidence that presently AC is not reliably diagnosed prior to the onset of significant fibrosis as well as data which demonstrate strong age skewing in the incidence of AC [11,12,20,73,74]. For example, White and colleagues found an 8% increased incidence of AC per decade of life in women but not men, whereas Vastamaki and co-workers reported a 10% increase in incidence of post-operative stiffness per single year of age in patients undergoing open rotator cuff repair [73,74]. Given the apparent current difficulty in reliably diagnosing the condition in the inflammatory stage prior to the onset of significant fibrosis and a subsequent protracted disease course, it has been suggested that AC should be clinically assumed until it is excluded and regularly monitored for development during management in the relevant age groups [12]. Further research which elucidates the effects of age skewing and sex on risk ratios for developing AC as well as establishing reliable and valid diagnostic criteria for early stage AC is likely to be of significant value the it's early detection, management, and potentially, prevention.

## Discussion

*AC pathophysiology and general inflammatory control mechanisms*

The inflammatory and fibrotic pathophysiology and of AC is highly consistent with current understanding of human inflammatory control mechanisms [1,3,8,9,46,48]. Without infection or significant tissue necrosis, pro-inflammatory signalling will tend to be limited and a chronic low grade inflammatory state potentiates

a holding pattern which often involves fibrosis of collagenous tissue as a storage depot for leukocytes and concurrent atrophy of parenchyma [8,9]. This is consistent with histological and magnetic resonance imaging studies of AC whereby the disease process appears to be cytokine driven which progresses from inflammation and hyperplasia of the synovium to capsular fibrosis with infiltration of chronic inflammatory cells and cytokines with a corresponding reduction of joint volume [1,3,46,48,65]. Evidence of increased presence of cytokines, mast cells, macrophages, lymphocytes, T and B cells in AC suggest both local and systemic signalling, although the precise mechanisms by which these could interact to facilitate the onset and progression of AC is yet to be fully elucidated [1–3,8,9,46,48]. Current mathematical models of systemic inflammation suggest involvement of covalent and ultrasensitive signalling cascades, thus a simple aggregation of local, segmental and systemic pro-inflammatory cytokine signalling potentiating the onset and progression of AC is a plausible conservative theoretical model consistent with the hypothesis, and potentially worthy of further investigation [75–79]. Interestingly, the pathophysiology of AC is largely self-limiting with seemingly full tissue and joint regeneration to pre-morbid levels, thus elucidating and harnessing the cytokine and immune signalling by which this is regulated in AC could hold diagnostic and therapeutic potential for other, less benign, inflammatory and fibrosing conditions [8,9].

*The extracellular matrix (ECM) and potential role of hyaluronic acid (HA) in AC*

Dense and loose connective tissues including joint ligaments, capsule, synovium and its fluid, are largely made up of ECM [60,80,81]. Hyaluronic acid (HA), a non-sulphated glycosaminoglycan is the primary component of the ECM, and has important functions in ECM-cell, and intracellular communication [82,83]. HA has fundamental roles in inflammation, mitosis, ECM adhesions, tissue repair and wound healing. HA in humans has high metabolic turnover, postulated to be due to it's role in scavenging free radicals and reactive oxygen species [82]. However, the functional role of HA appears to depend on its size with the larger native structure considered as anti-inflammatory and anti-mitogenic whereas the cleaved smaller fragments are considered pro-inflammatory and pro-mitogenic, also reportedly dependent on activation of the NF-κβ pathway [44,82–85]. Excessive metabolism of HA into its smaller fragments has strong associations with pathophysiological and morbid states such hyperglycaemia, hyperinsulinemia, diabetes and cardiovascular disease further suggesting an interaction with metabolic syndrome, chronic low grade inflammation, and potentially, AC [35,82–85].

Pro-inflammatory cytokine mediated increases in HA metabolism have been demonstrated in synoviocytes through NF-κβ dependent activation [84,86]. This has obvious implications for AC due to the high proportion of HA in synovial fluid and the intimate anatomy and function of the synovium and joint capsule [55,60,82,84,86]. Increased HA metabolism is associated with the formation of ECM adhesions and formation of ECM cable like structures, which are considered storage depots for leukocytes acting as mediators of inflammatory control mechanisms [8,9,82,84]. It is yet to be determined what relationships, if any, these HA related ECM adhesions have with the capsular fibrosis evident in AC. However, there is strong evidence that both local and systemic inflammatory mediators such as prostaglandins and pro-inflammatory cytokines facilitate upregulation of HA synthesis and cleavage facilitating deleterious ECM adhesions and fibrosis, which is largely consistent with the pathophysiology evident in AC and the hypothesis presented herein [1–4,8,9,46,48,82–86]. If dysregulation of HA metabolism was substantiated to have a significant role in inducing or perpetuating AC, novel treatments such as anti CD44 antibody therapy could become relevant and efficacious [82–85].

*Linking physical and mental health, the ECM and a potential central driver of connective tissue dysfunction?*

HA has also been demonstrated to activate kappa opioid receptors, which in a dysfunctional state, are strongly linked to pain and psychosocial stress states primarily through the ventral tegmental area, providing a direct link between psychosocial stress and ECM signalling [87–89]. NF-κβ pathway activation seemingly appears to be the common denominator between the pro-inflammatory cytokine mediated vascular micro and macro pathophysiology of mental and physical health dysfunction [38,43–45,47,84]. Given the aforementioned associations between NF-κβ activation and deleterious alterations in HA metabolism and the potential but likely role of HA in AC, this provides an area for further study which may help elucidate the signalling patterns involved in the onset of AC, which could eventually lead to improved management of the condition. For example, toll like receptor 2 and 4 are both a HA receptors and upstream regulators of NF-κβ pathway activation with known therapeutic potential in synovial joint disease, which could also be relevant in treating AC [82,86,90,91].

Lastly, metabolic syndrome and chronic low grade systemic inflammation also appear to be strongly associated with increased incidence and prevalence of central nervous system dysfunction and degeneration, with some evidence of causality [28,38,40,41,92–104]. Emerging evidence strongly supports a pervasive role of the ECM in these processes [7,10,50,105–108]. Furthermore, recent evidence suggests the choroid plexus functions as an important central 'educative gate' of inflammatory and immune signalling with also a seemingly ubiquitous involvement over a broad range of human pathophysiological states, including connective tissue dysfunction [109–113]. Furthermore, the choroid plexus is reported to have an intimate anatomical and physiological relationship with the limbic and para-limbic structures, a brain region chiefly involved in homeostasis and long term potentiation, which could potentially constitute a periventricular-limbic central driver of deleterious signalling cascades facilitating CT and ECM dysfunction [25,38,41,92,105–117]. This concept is supported by evidence of highly unique, persistent and robust signalling cascades around this anatomical region [118–120]. Given evidence of HA metabolic alterations in synovial fluid, serum and cerebrospinal fluid associated with joint pathologies, this suggests that it is not implausible to speculate that such a central driver, known to be implicated in CT and ECM dysfunction, could have a significant role in regulating inflammatory and neuro-immune signalling cascades involved with the onset, progress and eventual resolution of AC, potentially warranting further research [1,8,9,86,92,102,110,111,113].

## Conflicts of interest

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