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Periarthritis of The Shoulder: Pathophysiology, Pharmacological Management, And Emerging Therapeutic Approaches

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Abstract- Periarthritis of the shoulder, commonly known as frozen shoulder or adhesive capsulitis, is associated with pain, stiffness, and limited range of shoulder movement. The aim of this review is to discuss the condition's epidemiology, pathogenesis, diagnostic methods, and treatment. The condition is caused by inflammation, activation of fibroblasts, and formation of fibrous capsule, with diabetes being one of the major risk factors. NSAIDs, paracetamol, corticosteroids, physical therapy, and hydrodilatation are among the treatment options for this disease. Short-term treatment with intra-articular corticosteroids and long-term treatment with PRP may prove beneficial. Newer treatments which target inflammatory and fibrotic processes show promise in terms of future development. At the same time, there remain gaps in the clinical evidence and standardized treatment. Accurate diagnosis and stage-specific and personalized treatment are important for better functional outcomes. Further research in the form of randomized controlled trials is needed.

Keywords Frozen shoulder, Adhesive capsulitis, Periarthritis, Corticosteroids, Platelet-rich plasma, Physiotherapy.

I. INTRODUCTION

Shoulder periarthritis, also known as Duplay's disease (1896) and later as frozen shoulder (Codman, 1932) and adhesive capsulitis (Neviaser) is a painful fibro-inflammatory process of the glenohumeral joint capsule that involves stiffness and progressive reduction in range of motion of both active and passive shoulder (1). According to the definition of the American Academy of Orthopaedic Surgeons, it is defined as a condition that has a questionable etiology and a considerable restriction in active and passive ROM of the shoulder without any known primary shoulder disease. Codman described this condition as "difficult to define, difficult to treat, and difficult to explain from the point of pathology" (2). Over a period of more than a century, its underlying biology has remained mysterious, progressing from capsule inflammation to capsular fibrosis and contraction (3). This review covers modern data on the epidemiology, staging, molecular pathogenesis, clinical diagnosis, pharmaceutical and non-pharmaceutical treatment options, and novel therapies.

1. Epidemiology And Clinical Burden

This condition affects up to 2-5% of the general population with the peak incidence occurring between the ages of 40 and 60 (1). The estimated annual incidence in the general population is 3-5% with an increase to about 20% in patients suffering from diabetes (4). Periarthritis is 2-4 times more common in women than in men and affects predominantly middle-aged and elderly people (2).

The strongest and best-characterized risk factor is diabetes mellitus. Meta-analysis of 18 studies showed that patients with diabetes were 5 times more likely than the controls to have adhesive capsulitis. Pooled prevalence of adhesive capsulitis in patients with diabetes was 13.4%. The prevalence of diabetes in patients with adhesive capsulitis was 30%. Therefore, screening of diabetes is recommended in patients with adhesive capsulitis (5). In 2026, a systematic review and meta-analysis have shown 3.69 times higher risk of adhesive capsulitis in people with diabetes with other risk factors including poor glycemic control, obesity, hyperlipidemia, hypertension, thyroid disease, and smoking (6). Modern literature suggests that the prevalence of adhesive capsulitis in patients with diabetes is 3-10-fold higher than in non-diabetic patients and is associated with longer duration of diabetes and poor glycemic control (7).

Besides diabetes, other identified risk factors in large cohorts are obesity, younger age at diagnosis, and racial/ethnic disparity both in the development of the disease and access to surgical treatment (8). Secondary adhesive capsulitis develops after trauma, shoulder surgery, prolonged immobilization, rotator cuff disease, cardiovascular disease, hemiparesis, thyroid or autoimmune diseases (4)(9). The clinical burden is significant since symptoms usually persist for 18-30 months, and painful reduction in the range of motion does not resolve completely for several years (3), leading to disability, occupational disruption, and higher

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medical cost. This burden is especially significant in the regions with a high prevalence of type 2 diabetes (10).

2. Classification And Stages

Adhesive capsulitis can be either primary (idiopathic), which means there is no underlying cause, or secondary due to trauma, surgery, immobilization, or systemic diseases such as diabetes and thyroid disorders (9). From a clinical standpoint, the disease develops through three typical stages:

- Freezing (painful/inflammatory) stage: Increasing pain, especially at night and during activities, along with gradual stiffness.
- Frozen (adhesive/stiffness) stage: Pain is relieved at rest; however, there is a restriction of both active and passive motion. The adhesions occur in the capsule and surrounding tissue, which limits joint mobility (11).
- Thawing (resolution) stage: Slow recovery of motion over months to years (12)(13).

The stage affects the treatment efficacy: according to a network meta-analysis of 92 randomized trials, the combination of intra-articular steroid injection and traditional physiotherapy produces the most significant improvement in the painful freezing stage; joint manipulation is more effective in the adhesive stage. Stage, and diabetes are possible factors moderating the outcomes (14).

3. Pathophysiology

Frozen shoulder is an inflammatory and fibrotic disorder of the glenohumeral capsule (10); its development is associated with a sequential process of synovial inflammation and capsular fibrosis (3). Histologically, the capsule demonstrates nonspecific chronic inflammation with an increase in the number of fibroblasts, myofibroblasts, adipocytes, and vessels (15). The current pathogenesis assumes that the initial injury to the shoulder leads to an increase in growth factor and cytokine levels, increased turnover of the extracellular matrix, myofibroblast activation with collagen deposition, and decreased matrix degradation (15).

A predisposing inflammatory or metabolic state, such as diabetes and hyperlipidemia, can further aggravate the above abnormalities (15). Metabolic derangement associated with low-grade inflammation, insulin resistance, and neuroimmune interaction has also been suggested as one of the multifactorial causes of the disease (16). Importantly, an inflammatory stage of the condition is potentially reversible: early intra-articular corticosteroid treatment can interrupt the inflammatory cascade and prevent fibroblast-to-myofibroblast transition, but not reverse the fibrosis that is already present. This provides a rationale for early treatment instead of "supervised neglect" (17).

4. Molecular And Inflammatory Mechanisms

Cytokines and growth factors released by immune cells affect the actions of the fibroblasts; on the other hand, matrix turnover is affected by matrix metalloproteinases (MMPs) and their inhibitors (18). Some important studies include the following:

Activated fibroblasts: The fibroblasts of frozen shoulder capsule display the expression of activated cell markers (CD248, CD146, VCAM, PDPN), increased levels of IL-6, IL-8 and CCL-20. Activation of control fibroblasts by IL-1β can be used as evidence for the activated stromal fibroblasts' role as starters and maintainers of inflammation (19).

Macrophage-fibroblast interaction: Single cell atlases describe a CD48+IL1A+ macrophage population in the rotator interval, secreting IL-1α and IL-1β. As a result, the fibroblasts become activated through IL-1R to express inflammatory genes (CCL2, CCL5, IL-6) and fibrotic genes (TGFB1, WNT5A, COL3A1). The IL-1R signaling pathway may be a treatment target (20).

Pro-inflammatory molecules and decreased MMP: Consistently high level of pro-inflammatory mediators, decreased amount of MMP and increased level of activators of fibroblast activation and nerve growth was found through molecular research studies (15). Some of the pro-inflammatory molecules that are involved in inflammation are COX-1, COX-2, IL-1, IL-6 and TNF-α in connection with adhesion, edema, pain and changes in the disease activity (21).

Alarmins and pain: Upregulated HMGB1, IL-33, S100A8 and S100A9 were found in frozen shoulder capsule along with marked increase of the neoinnervation associated with the patients' reports of pain. Cellular stress-induced release of HMGB1 may sustain inflammatory response of the tissue (22).

5. Clinical Presentation And Diagnosis

Diagnosis is clinical and involves spontaneous onset of severe shoulder pain interfering with daily activities and sleep, along with progressive limitation of active and passive movements, especially elevation and external rotation (23). Capsulitis may be abrupt or insidious, with the arm in adduction position, generalized limitation of shoulder joint movement, and pain extending to the pectoral, deltoid, and infraspinatus muscles. Inflammation and contracture of the capsule lead to progressive stiffness and loss of movement (11).

Imaging is not required for diagnosis (24). Radiographs are usually normal and help rule out other diagnoses, while MRI may show thickened capsule, synovitis, and capsular edema. Coracohumeral ligament thickening on non-contrast MRI has high specificity (24)(25). Ultrasound imaging is increasingly being used, including dynamic, contrast

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enhanced, and sonoelastographic evaluation of the capsular thickness (10). Because of the bidirectional relationship with diabetes, screening for diabetes is advised for patients with adhesive capsulitis (5).

II. DRUG TREATMENT

1. Nsaids

NSAIDs are used in the early stages of disease for pain and inflammation, but they do not seem to affect the disease course alone. In a network meta-analysis of early stage, pain-predominant frozen shoulder, oral NSAIDs (2 RCTs, 44 participants) were not more beneficial than physical therapy in 12 weeks for pain or functional outcome (26). Direct comparison data indicate superiority of injections: one non-image guided intra-articular corticosteroid injection was associated with quicker pain relief and recovery of function and ROM compared to oral NSAIDs (27). Thus, NSAIDs are used as short term adjunctive analgesics with consideration of potential adverse effects on the GI tract, kidneys, and heart.

2. Paracetamol (Acetaminophen)

The drug paracetamol is often used as first-line simple analgesia in algorithms that start with analgesics, NSAIDs, physiotherapy and injection of corticosteroids (28). Indeed, the most detailed pharmacological network meta-analysis of intra-articular corticosteroids, intra-articular PRP, oral NSAIDs, and intra-articular hyaluronate showed no included trials of paracetamol (26). Thus, the disease-specific efficiency of paracetamol in adhesive capsulitis relies on practice alone. Paracetamol may still be considered a treatment option in cases when NSAIDs should not be used for any reason, keeping in mind the danger of developing liver disease and hepatotoxicity.

3. Oral Corticosteroids

Randomized, double-blind, placebo-controlled study conducted on prednisolone in dosage of 30 mg per day during three weeks found that in comparison with placebo, there was a significantly higher level of improvement in all parameters such as pain, disability, active ROM and self-ratings of improvement at three weeks. At six weeks, the benefits of prednisolone were more pronounced but they did not have statistical significance while the advantage of placebo appeared at 12 weeks (29). Cochrane-based studies confirm that the oral steroids show significant short-term benefits in terms of pain, ROM, and function but the effect is gone after 6 weeks (30).

4. Intra-Articular Injection Of Corticosteroids

The common practice is to use the intra-articular injection of triamcinolone that demonstrates fast pain-alleviating effects along with other advantages in short-term perspective (in particular, in diabetic people). Network meta-analysis on the early stages of the disorder confirms the advantage of corticosteroids over physical therapy at 12 weeks concerning both pain and function (8 randomized controlled trials, 340 patients) (26), and non-surgical network meta-analysis places steroid injections among the most effective interventions concerning both pain and function (14). The timing is crucial: early treatment is associated with shorter symptom duration and higher functional score (25), while the earlier the treatment is initiated within the disease process, the better since it is possible to affect the inflammatory cascade before the formation of fibrosis (17). The techniques and dosages can be adjusted (e.g., using the rotator interval and low dose of corticosteroids (10 mg compared to 40 mg)) for better pain relief and function (25). However, the results of treatment are frequently temporary; moreover, the repeated treatment is associated with the danger of cartilage damage, weakening of the tendons, transient hyperglycemia, and suppression of the hypothalamic–pituitary–adrenal axis (10). Botulinum toxin type A demonstrated the equivalence to triamcinolone for short-term pain and range of motion without the emergence of adverse events according to the referenced paper (31).

5.Analgesics Combination And Multimodal Pharmacological Treatment

As one pharmacological substance does not change the full course of disease, multimodal strategy remains an actual choice of practice including basic analgesia with NSID use during inflammatory stage where possible, intra-articular corticosteroids as an early intervention in pain-related freezing-stage disorder, and physiotherapy (14). Additional analgesia may be achieved via the use of suprascapular nerve blocks in combination with intra-articular injections (32). In a comprehensive network meta-analysis, physical therapy along with either medical treatment or ultrasound shows good results concerning pain relief (33). The combination of interventions should be selected based on the disease stage, gender, presence of diabetes, and other risk factors (14).

6. Non-Pharmacological Management

Physical therapy plays a crucial role in treatment and is most efficient in combination with other treatments depending on the degree of irritability and intensity of symptoms (34). Other options include short wave therapy, ultrasound therapy, transcutaneous electrical nerve stimulation, and hydrotherapy (1).

Hydrodilatation (hydraulic capsular distension) allows improving early mobility due to mechanical distension of the capsule (32). Ultrasound-enhanced hydrodistension, along with specific exercises, was shown to improve pain, disability and ROM in stage 1 and 2 disease in particular when diagnosed before stage 2 (13). Capsular distension was

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found to have significant impacts on pain and functioning among non-invasive interventions in a network meta-analysis (14).

Extracorporeal shock wave therapy (ESWT) affects inflammation and might promote tissue repair and functional improvement. ESWT is of special interest for diabetics since it is free from metabolic side-effects of corticosteroids; however, more comparative data is needed (35)(25).

Suprascapular nerve block (SSNB) is an analgesic augmentation for intra-articular therapy and might help in rehabilitation (32).

Manipulation under anaesthesia (MUA) is beneficial for ROM, pain and functioning in selected patients. Selected criteria include stage 2 disease, external rotation less than 50% of the contralateral shoulder, conservative treatment failure, and at least 6 months of conservative treatment including injections and physical therapy (17).

Arthroscopic capsular release can be used after conservative treatment failure after about 9-12 months and might be beneficial for ROM improvement. It also allows visualization of the capsule. This procedure might be used in case of treatment refractoriness but has certain procedural risks that should be compared to non-surgical treatment and MUA (33)(25).

7. Emerging And Novel Pharmacological Approaches

The molecular dissection of frozen shoulder is identifying novel therapeutic targets.

Platelet-rich plasma (PRP): Intra-articular PRP has shown benefits over physical therapy for pain, function, and ROM at 12 weeks in early-stage disease (26). A meta-analysis of 14 RCTs (1,024 patients) showed that PRP was better than controls in terms of visual analog scale (VAS), Disabilities of the Arm, Shoulder and Hand (DASH), Shoulder Pain and Disability Index (SPADI), and ROM, with good safety profiles (36). Another meta-analysis of 13 RCTs (1,056 patients) has shown PRP superiority over corticosteroids at six months for VAS (mean difference [MD] −1.84), DASH at three and six months, and for abduction, external rotation, and internal rotation, with generally similar results at one to three months (37). Randomized head-to-head trials have also shown better long-term pain and disability scores with PRP versus methylprednisolone at 24 weeks (4). In a PROBE-design trial, triamcinolone had better short-term outcomes, while PRP had better long-term VAS and DASH outcomes (1). Lack of homogeneity of PRP products is a limitation (38).

Hyaluronic acid (HA): Intra-articular HA was not beneficial compared to physical therapy in early-stage network meta-analysis (26); however, a meta-analysis of seven RCTs showed similar outcomes to corticosteroids at six and 12 weeks, although corticosteroids were better at two to four weeks. HA can be used as a steroid-sparing treatment in selected patients who are at risk of adverse effects from corticosteroids (39).

Anti-TNF biologic therapy: Due to TNF-α overexpression in the capsule, a multicenter randomized, double-blind feasibility study is testing intra-articular adalimumab (160 mg, followed by 80 mg at two to three weeks) versus saline placebo in early-stage pain-predominant frozen shoulder (40).

IL-1 pathway inhibition: Identification of CD48+IL1A+ macrophages driving fibroblast activation through IL-1R makes IL-1R axis a candidate therapeutic target (20).

TSG-6 (TNF-stimulated gene-6 protein): Recombinant TSG-6 decreases proliferation of human frozen-shoulder capsule fibroblasts and downregulates COL1A1, TNF-α, IL-6, and IL-1β through inhibition of the TGF-β/Smad2 pathway (41).

Tetrandrine: In a rat model of frozen shoulder, tetrandrine prevented capsular angiogenesis, collagen remodeling, and fibrosis and inhibited the TGF-β1/Smad pathway, making it a candidate for prevention and therapy (42).

BoNT-A: Intra-articular BoNT-A was found to be comparable to triamcinolone in terms of short-term pain and ROM and was suggested as a steroid-sparing alternative or second-line treatment (31).

Other agents: Systematic reviews identified hyaluronan, TSG-6, tetrandrine, and cannabidiol as potential agents acting on the same inflammatory and fibrotic pathways in preclinical studies (43). Salmon calcitonin could inhibit the production of fibrosis-related factors in capsular fibroblasts, and PPAR-γ agonists were evaluated in rat models. Pulsed radiofrequency is another neuromodulatory technique targeting pain (32).

III. COMPARATIVE EVALUATION OF AVAILABLE TREATMENTS

Based on the available trial evidence, intra-articular corticosteroid injections have proven to be the quickest and most effective short-term treatment during the pain-dominant stage. They outperformed oral NSAIDs in comparison studies (27) and provided superior results compared to physical therapy alone after 12 weeks in early stages of the disease (26). Oral corticosteroids have a short-term effect, which is lost by about six weeks (29). Hyaluronic acid (HA) could be inferior to corticosteroids in the first two to four weeks but could achieve comparable results by six to 12 weeks (39). In the long term, PRP showed better outcomes than corticosteroids regarding pain, function, and ROM at six months in meta-analyses (37)(4); however, variations in the PRP formulation and methodology of the trials make it

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necessary to interpret the results with caution (36)(38). Stage-based treatment involves injection and physiotherapy during the freezing stage, manipulation during the adhesive stage (14), and hydrodilatation before the development of motion restriction (13). Manipulation under anesthesia (MUA) or arthroscopic release could be considered for refractory cases. While surgical treatments might have the highest outcomes in terms of ROM, none of them dominates in other parameters (33). In diabetic patients, ESWT could be used as an additional treatment to avoid metabolic effects of steroids (25). HA or BoNT-A could be another potential steroid-sparing option in some patients (31)(39).

IV. CHALLENGES AND EVIDENCE GAPS

Several factors limit the quality of clinical care. Firstly, there is an incomplete understanding of the etiology and pathogenesis, as well as a lack of consensus on the most effective treatment (3). Also, frozen shoulder is seen as a diagnostic group which could benefit from more precise criteria (10). Secondly, the evidence in question is heterogeneous and potentially biased. The network meta-analysis suggests caution when interpreting the results on the use of intra-articular corticosteroids and platelet-rich plasma (PRP) because of the risk of bias, heterogeneity, and inconsistency (26). PRP meta-analyses show significant heterogeneity with the I^2 values over 50% in some cases and the non-standardized PRP formulations (38). Thirdly, the use of simple oral analgesia is under-studied. Oral NSAIDs were tested in only two small RCTs with 44 participants, and no paracetamol trial was found in the pharmacological network meta-analysis (26) despite its wide usage in practice (28). Fourthly, the results of the basic science research are not consistent and inconclusive, and the need for the standardized protocols and clear criteria for different stages of the disease is needed before the cytokines, growth factors, matrix metalloproteinase (MMP), and immune cells findings could be translated into the clinical target (18). Reliable experimental models for the disease are needed as well (3). Fifthly, the idea of a self-limiting natural history has been refuted by the evidence of functional limitations in some patients (24); however, natural history and prognostic factor research is lacking (17). Sixthly, the association between diabetes and adhesive capsulitis may be confounded by other factors. There is a need for high-quality longitudinal studies on causality and mechanisms of this phenomenon (6).

1. Future Prospects

The future trend in the area is the mechanism-specific and stage-specific treatment strategy. Detailed understanding of disease pathology at distinct stages will reveal the mechanisms of regulation of inflammation and fibrosis, and provide new targets for treatment (18). With the single cell atlasing, omics profiling, and spatial technology, a better roadmap of fibroblast heterogeneity and macrophage-fibroblast interactions will be obtained, nominating IL-1R to be a potentially druggable pathway (20)(44). On the other hand, proof-of-concept trials of biological treatment of early stage of adhesive capsulitis are being carried out in the form of an intra-articular anti-TNF (40). Some preclinical drug candidates targeting TGF-β/Smad signalling such as TSG-6 and tetrandrine may become tools for prevention of the formation of capsular fibrosis, however, they have not been evaluated clinically yet (41)(42).

From the clinical point of view, some priorities are the well-designed RCTs to test injections versus standardized physiotherapy or placebo (26), standardization of PRP treatment (38), studies on predictors of natural progression of the disease (17), and personalized treatment based on the disease stage, the diabetic condition, and injection target (14)(32).

Considering the close relation of adhesive capsulitis to type 2 diabetes, early diagnosis and treatment should become an important goal. Early identification of the condition, individualized pain management, and rehabilitation depending on the disease stage might assist in decreasing long-term disability.

V. CONCLUSION

Periarthritis of the shoulder is a complex disorder requiring timely diagnosis and personalized stage-by-stage treatment. Corticosteroid injection therapy is useful for short-term treatment, while platelet-rich plasma (PRP) is helpful for long-term benefits. Physiotherapy is necessary to improve the movement and functioning of the shoulder joint. Novel treatment approaches targeting inflammation and fibrosis might be more successful in the future. Nevertheless, more clinical trials are needed for development of treatment methods.

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