Clinical Management of Arthrofibrosis

State of the Art and Therapeutic Outlook

Ishaq O. Ibrahim, MD

Ara Nazarian, PhD

Edward K. Rodriguez, MD, PhD

Investigation performed at Beth Israel Deaconess Medical Center, Boston, Massachusetts

Abstract

» Arthrofibrosis is a pathologic condition that is characterized by excessive periarticular scar-tissue formation. Arthrofibrosis may occur secondary to injury, surgical trauma, hemarthrosis, or infection, or it may occur idiopathically.

» The pathogenesis of arthrofibrosis is incompletely understood but involves the dysregulation of normal reparative pathways, with transforming growth factor-beta (TGF-β) as a principal mediator.

» Current treatment options for arthrofibrosis primarily involve physiotherapy, operative manipulation, and surgical debridement, all with imperfect results.

» Currently, there are no pharmacologic treatment options for arthrofibrosis. This has prompted increased investigational interest in the development of antifibrotic intra-articular therapies.

Arthrofibrosis (AF) is a pathologic condition that is characterized by excessive periarticular scar-tissue formation, resulting in joint stiffness and soft-tissue contractures[1]. Periarticular fibrosis, driven by excess collagen production and deposition of extracellular matrix (ECM) within the joint capsule and the surrounding tissues, impairs functional joint motion, leading to difficulties in completing activities of daily living (ADLs). AF may occur secondary to injury, surgical trauma, hemarthrosis, or infection, or it may occur idiopathically. AF presents a serious limitation for patients and continues to pose challenges for clinicians who are tasked with its prevention and treatment[1]. In addition to loss of motion, patients commonly experience chronic pain and swelling; they are often treated with prolonged periods of physiotherapy, with uncertain and inconsistent outcomes.

AF represents a broad spectrum of disease, the clinical implications and sequelae of which are encountered by orthopaedic specialists in various clinical contexts. While AF can occur in most joints, the knee is the most common site where it may occur in a surgical orthopaedic setting secondary to cruciate ligament reconstruction surgery, total knee arthroplasty (TKA), or osteosynthesis of periarticular fractures[2-4]. The goals of this review are to provide an up-to-date report on the current understanding of AF, review the most commonly encountered forms of AF in the orthopaedic clinic, describe currently available treatment options, and explore therapeutic outlooks and future directions for the treatment of AF.

Pathogenesis

AF is a fibrosing disorder of the synovial membrane[5]. The pathophysiology of AF is incompletely understood but involves the aberrant proliferation of collagen, ECM, and, often, heterotopic bone within the involved joint and the surrounding soft tissues[1,4]. Several cytokines and growth factors are implicated in the pathogenesis of

Disclosure: The authors indicated that no external funding was received for any aspect of this work. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSREV/A614).

AF. These include, but are not limited to, interleukin (IL)-1, IL-6, and IL-17, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), β-catenin, and bone morphogenetic protein (BMP)-2[1,5,6].

AF results from dysregulation of reparative cascades that are involved in adaptive immunity and healing[1]. TGF-β, a ubiquitous signaling protein with well-described roles in physiologic tissue repair and scar formation, has been identified as the primary driver of fibrosis[1,7,8]. Tissue injury induces production of TGF-β and other proinflammatory cytokines that further drive the inflammatory cascade and ultimately lead to the activation and differentiation of myofibroblasts, which in turn produce ECM. TGF-β also contributes to fibrosis by inducing transcription of the COL1A1 and COL1A2 genes that encode type-I collagen, the most abundant component of a fibrotic scar. Failure of apoptosis and autophagy results in excess deposition of dense fibrous tissue within the joint and the periarticular tissues[9]. The underlying cause for dysregulation, however, remains uncertain. The profibrotic activity of β-catenin also is well-recognized through its previously described role in upregulating cell proliferation through activation of the Wnt pathway[6]. The presence of BMP-2 in immunohistochemical specimens suggests that endochondral ossification and heterotopic bone formation also may contribute to the loss of motion that is observed in patients with AF[10].

Common Orthopaedic Clinical Presentations

Knee Ligament Reconstruction

AF is a well-described complication of anterior cruciate ligament (ACL) reconstruction surgery, with reported rates as high as 35% to 38%[2,6]. The prevalence of AF is greater with multiligamentous knee injuries resulting from higher-energy injury mechanisms, which produce a greater degree of soft-tissue damage[11,12]. As such, motion loss is most common after traumatic knee dislocation, with rates of postoperative stiffness as high as 57%[13]. Postoperative motion loss in this patient population is particularly devastating and associated with poor outcomes and substantial patient dissatisfaction. Persistent losses in knee motion also have been associated with higher rates of osteoarthritis[6].

Normal knee motion involves 3 sub-arcs of motion consisting of terminal extension, active flexion, and passive flexion[11]. The terminal extension arc permits the knee to lock (the so-called "screw-home" mechanism), allowing the quadriceps to relax during stance[14,15]. The functional motion arc of the knee is from 10° to 120° and encompasses the range that is required for most daily activities. Motion loss in the knee is of variable consequence depending on the patient's functional demands and premorbid level of function. Even minor losses of motion, however, are poorly tolerated in young and active patients. Losses in flexion are better tolerated than losses in extension, which require chronic quadriceps activation to maintain stance and increase contact forces along the patellofemoral joint[16].

Both preventative and interventional treatment strategies for AF that is associated with ligament reconstruction have been extensively studied in the literature. Several risk factors for AF are described, including technical errors in graft placement, concomitant extra-articular procedures (e.g., combined medial collateral ligament reconstruction), infection, prolonged immobilization, and timing of surgery[17]. Common technical errors include anterior tibial tunnel placement, leading to graft impingement in extension, and excessive anteromedial placement, which ultimately limits flexion[11,17,18]. The literature regarding the timing of ACL reconstruction is controversial[19-22]. A 3 or 4-week delay in reconstruction after injury has been shown to reduce rates of AF following ACL surgery[23]. Delaying reconstruction is speculated to decrease concentrations of inflammatory mediators and profibrotic signaling proteins prior to exposing the knee to additional insult. Some studies have indicated a greater effect of preoperative range-of-motion training (in particular, achieving full extension) on postoperative motion and overall patient outcomes. Modern perioperative and rehabilitative protocols have allowed patients to reclaim motion at high rates. Despite this, a small subset of patients ultimately requires secondary operations, including lysis of adhesions (LOA) and revision reconstruction to address postoperative stiffness[24,25].

Lysis of Adhesions

Both localized and global forms of AF have been described after ACL reconstruction[26]. In the localized form, increased soft-tissue volume is restricted to the anterior compartment of the knee. A "cyclops" lesion, or soft-tissue nodule anterior to the tibial insertion of the ACL, often is present and impedes full knee extension[26,27]. In the global form, fibrosis is more extensive and generally involves the suprapatellar pouch and gutters[26]. In a prospective study by Aglietti et al., only 37% of patients with global forms of AF had a satisfactory outcome following open or LOA[26]. Once AF has been diagnosed, earlier surgical intervention has been associated with improved outcomes[28]. For patients in whom LOA is unsuccessful, revision reconstruction is the final option to salvage knee motion.

Total Knee Arthroplasty

AF is a leading cause of failure following TKA[4]. AF accounts for up to 10% of TKA revisions that are performed within 5 years of surgery and 28% of hospital readmissions after knee replacement[4]. As such, the individual and economic burdens of AF after TKA are substantial. Up to 25% of patients undergoing secondary surgical procedures require >1 operation for persistent stiffness[29].

Postoperative knee range of motion of 0° to 110° after TKA is considered functionally adequate and is an accepted indicator of successful knee arthroplasty[30]. Excessive scar-tissue

formation within the joint capsule and the periarticular tissues limits knee motion and predisposes to soft-tissue contracture[4]. Even minor losses in knee extension increase energy expenditure during gait. Performing ADLs, higher-order activities such as driving, or even sitting and walking may become difficult or impossible because of AF.

The etiology of AF after TKA is unclear. Several perioperative and patient factors are speculated to increase the risk of scar-tissue proliferation in the postoperative period[31]. Preoperative risk factors include poor range of motion, poor pain tolerance, prior knee surgery, complex primary arthroplasty, and possible genetic predisposition[32]. Poor preoperative range of motion is a critical risk factor for AF after TKA. Similarly, component oversizing and malpositioning have been shown to increase the risk of stiffness postoperatively. Extension of the femoral component may limit the knee flexion arc, while component flexion may prevent full extension. Additionally, component and soft-tissue imbalances as well as incomplete osteophyte resection may contribute to poor range of motion after surgery.

Multiple studies have indicated a genetic predisposition to AF; this recently has garnered interest in the potential for a genetic predisposition to knee stiffness after TKA[32]. Genetic polymorphisms in genes that encode profibrotic cytokines such as TGF-β have been examined and have been shown to be associated with increased fibrotic risk in the liver and the lungs[33,34]. Additional research in this area may permit the development of patient screening tools and mechanisms to customize treatment protocols on an individual patient basis in an effort to maximize outcomes[4].

Physiotherapy is the primary modality for the prevention and treatment of AF that is associated with TKA. Optimizing knee range of motion and quadriceps strength in the preoperative period has been shown to improve functional outcomes and patient satisfaction after knee replacement[35,36]. Early and aggressive physiotherapy as soon as feasible after knee replacement also has been shown to limit the rate of post-TKA AF[37].

Manipulation Under Anesthesia

Manipulation under anesthesia (MUA) is the preferred treatment for post-TKA stiffness that has not responded to physiotherapy[38]. Specific indications for and timing of MUA are not standardized and vary in the literature and in clinical practice. MUA is most effective if performed within 3 months of surgery, presumably prior to scar-tissue maturation and contracture formation[31]. Recent studies have demonstrated an inverse relationship between the timing of MUA and final range of motion after manipulation[39]. Despite some controversies specific to the practice of MUA, such as indication and timing, it remains widely accepted as the first-line treatment for post-TKA AF.

MUA is typically performed under general anesthesia. Addition of a paralytic agent to facilitate muscle relaxation may be given at the discretion of the surgeon and the anesthesia team. The hip is generally flexed to 90°, and gentle steady pressure is exerted to flex the knee while grasping the tibia proximally to limit the lever arm on the joint. The procedure is completed when the surgeon is no longer able to feel or hear adhesion separation and a satisfactory improvement in range of motion has been achieved. Aggressive manipulation, however, may generate an inflammatory response and produce additional scarring. As such, some authors have recommended preoperative administration of intravenous glucocorticoids and perioperative oral glucocorticoids, as well as use of a continuous passive motion (CPM) device in the postoperative period. However, evidence for the efficacy of these measures in improving range of motion following MUA is limited.

Mean improvement in range of motion following MUA is approximately 30° to 47°[4]. Longer-term follow-up studies have reported a mean improvement in range of motion of approximately 30° at 10 years of follow-up[40]. Repeat MUA has been associated with mixed results, and consensus regarding its effectiveness has not been reached[31,41].

Static progressive stretching devices, including the JAS brace (Joint Active Systems), and, more recently, the STAK (Self Treatment Assisted Knee Flexion) tool, may provide patients with an alternative noninvasive treatment modality with similar efficacy to MUA[42,43]. Static progressive devices can be powerful adjuncts to physiotherapy. An early clinical study evaluating the efficacy of the STAK tool in patients with post-TKA AF observed a mean improvement in knee flexion of 30°, with similar improvements in knee outcome scores at a mean of 10.5 weeks[43].

Lysis of Adhesions

Patients with persistent stiffness despite aggressive physiotherapy and/or MUA may benefit from arthroscopic or open LOA. Moderate improvements in both extension and flexion have been described after arthroscopic LOA[44,45]. Open LOA has demonstrated similar efficacy, but with increased risk of wound complications, extensor mechanism injury, and deep infection. Arthroscopic and open LOA have yielded similar results to MUA and are rarely employed in clinical practice[46].

Revision Arthroplasty

As a last resort, revision TKA may be necessary to address refractory post-TKA stiffness. Revision TKA also should be considered in cases of overt component malpositioning. Outcomes of revision TKA for AF have been sparsely examined in the literature, and the few studies examining outcomes in this patient population have found outcomes to lag behind those for patients undergoing revision TKA for other indications, including infection, loosening, and wear. Furthermore, AF is likely to develop again after revision TKA, and >25% of patients undergoing revision TKA may ultimately require a second revision to address persistent stiffness[23].

Periarticular Fractures

Anatomic reduction and stable fixation of periarticular fractures is critical for successful healing and for minimizing the rate of posttraumatic arthritis. In this regard, postoperative practices historically involved lengthy periods of immobilization in an effort to prevent late fracture displacement. Prolonged immobilization, however, is now understood to predispose to AF, and practice habits have evolved in favor of rigid fixation and early motion[3].

The severity of impairment that is present once AF develops depends heavily on the joint that is involved and the degree of functional motion that is lost[3]. Risk factors for AF following periarticular fracture fixation are numerous, and few, in fact, are modifiable. In addition to prolonged immobilization, additional well-described risk factors for AF include high-energy injury mechanisms, external fixator use, and infection[3].

Proximal Humeral Fractures

The semiconstrained nature of the shoulder allows for an impressive breadth of motion. As a result, a well-functioning shoulder may compensate for motion losses occurring in other areas of the upper limb. The functional range of motion of the shoulder is fairly restrained in comparison with the true limits of glenohumeral motion. Just 120° of forward flexion, 130° of abduction, and 60° of external rotation are required to perform most ADLs. On the other hand, a well-functioning glenohumeral joint can achieve approximately 170° of forward flexion, 180° of abduction, and 100° of external rotation.

Early passive and active-assisted motion are the mainstays of modern rehabilitation protocols because of poor tolerance for antigravity motion and weight-bearing before fracture-healing. Modest motion loss is expected following internal fixation of proximal humeral fractures but is usually of limited functional consequence. In cases where motion loss exceeds the functional range, patients may be able to accommodate satisfactorily through the elbow and the wrist. Scapular substitution, whereby patients with painful or stiff shoulders achieve functional motion through the scapulothoracic joint, may occur as a result of scapular recruitment early in the recovery period[47]. This may offer a patient effective shoulder motion at the expense of abnormal motion through the scapulothoracic joint, and recovery of true glenohumeral motion may become more difficult secondary to altered scapular mechanics[48].

Nonetheless, AF is uncommon after fixation of proximal humeral fractures. For the rare cases that do arise, MUA is not recommended because of the high risk of fracture. Arthroscopic capsular release has been shown to be effective in improving range of motion. In 37 patients with poor range of motion after locked plating, Katthagen et al. reported a 122% increase in forward flexion, a 126% increase in abduction, a 140% increase in external rotation, and a 140% increase in internal rotation at 24 months following arthroscopic capsular release[49]. Aside from continued physiotherapy and arthroscopic capsular release, treatment options for motion loss after proximal humeral fracture fixation are limited.

Periarticular Elbow Fractures

In comparison to the shoulder, the elbow is a highly sensitive and "unforgiving joint."[3,50] Common traumatic elbow injuries include isolated fractures of the distal aspect of the humerus, the olecranon, and the radial head, as well as combined osseous and ligamentous injury, classically in the form of the "terrible triad" injury, which involves injury to the radial head, the coronoid process, and the lateral ulnar collateral ligament (LUCL)[51]. A modest degree of motion loss is expected following most elbow trauma, and terminal extension rarely is recovered[52].

A 100° arc of elbow motion is important for independence with most ADLs. Physiologic elbow motion averages 0° of extension to 146° of flexion[3]. Modest losses in elbow extension are generally well-tolerated as long as sufficient elbow flexion remains to permit independence in hygiene and feeding. Rigid fixation of periarticular elbow fractures permitting early rehabilitation is necessary for preventing AF following elbow trauma[3]. Osteoporosis and bone loss, however, present frequently encountered challenges during fixation of elbow fractures. As a result, construct stability may not always be sufficient to permit early motion as excess motion through the fracture site may predispose to nonunion and fixation failure.

Periarticular Knee Trauma

As previously discussed, full knee extension is critical to economizing energy expenditure during stance. Fractures about the knee may contribute to motion loss through AF or malunions that alter the mechanical axis of the lower limb in the sagittal plane[3]. In rare instances, the quadriceps muscle also may become adhered to the femur, restricting knee flexion. This particular complication has been associated with femoral external fixator pin placement or extensive elevation of the quadriceps muscle during surgical fixation[3].

The functional range of motion of the knee is variable depending on the tasks that are required and the needs of the patient. Approximately 98.5° of knee flexion is required to ascend stairs with a reciprocal gait[3,53]. This motion arc permits a normal gait pattern and allows a patient to rise from a chair, which require approximately 63° and 93° of flexion, respectively[3,54]. Therefore, range of motion from full extension to at least 100° of flexion after treatment of periarticular knee fractures is desirable[3]. Additional knee flexion is required for more specific activities such as rising from a low chair, which requires 105° of flexion, and exiting a bathtub, which requires 138° of flexion[3,53].

A 30° to 40° loss in knee flexion is common following fixation of supracondylar femoral fractures[3]. Still, the majority of patients who are treated for supracondylar femoral fractures achieve 0° to 1° of knee extension and

approximately 100° of knee flexion, allowing for independence with most ADLs[3]. Motion outcomes following open treatment of tibial plateau fractures are similar[55,56].

If stiffness persists despite aggressive physiotherapy, MUA may be effective in improving knee range of motion following open treatment of distal femoral and tibial plateau fractures. The timing of MUA has been shown to influence outcome; earlier MUA is associated with greater and more durable improvement in motion. Generally, fracture-healing should be complete prior to MUA, and MUA should be performed prior to concomitant implant removal to prevent fracture through vacant screw holes. Open release and quadricepsplasty are additional options for severe cases that are unresponsive to manipulation[57,58].

Adhesive Capsulitis

Adhesive capsulitis, known more broadly as frozen shoulder syndrome (FSS), is a pathologic condition that is characterized by pain and restriction of both active and passive shoulder motion in the setting of normal radiographs. The pathophysiology of FSS is incompletely understood but is believed to occur secondary to inflammatory and fibrotic processes occurring within the glenohumeral joint. Two primary forms of FSS are described. Primary idiopathic frozen shoulder is most common and occurs without discernible cause. Secondary frozen shoulder, in which there is a predisposing disease or injury process, carries a poorer prognosis[59]. While widely considered a benign self-limited condition, the disease course may last for up to 2 years and often results in some degree of permanent motion loss[59].

Capsular contracture is the principal feature of FSS. Fibrosis occurs secondary to imbalances in fibroblast activity and collagen degradation by matrix metalloproteinases (MMPs), resulting in overproduction of ECM as is observed in other fibrosing disorders. As in histological samples of joints with AF, increased levels of TGF-β and PDGF have been identified in patients with FSS, suggesting activation of a similar fibrosing cascade[60,61]. The pathogenesis of frozen shoulder also involves inflammatory mechanisms, which may ultimately stimulate fibroblast proliferation.

Loss of passive range of motion, most commonly external rotation, is key to differentiating FSS from other disorders of the shoulder. Pathoanatomically, FSS may be characterized by anterosuperior capsular contracture secondary to scarring through the rotator interval, producing stiffness in adduction, or anteroinferior contracture, which limits external rotation in abduction[59]. Shoulder radiographs are characteristically normal despite often marked shoulder stiffness. The disease course involves 3 poorly defined stages of variable length: the "freezing" stage, which is characterized primarily by pain and restricted motion; the "frozen" stage, which is predominantly defined by stiffness; and the "thawing" stage, during which motion returns and the symptoms primarily resolve. While considered "self-limited," the disease process often is protracted, with residual motion loss and a high rate of recurrence[59].

Physiotherapy, primarily involving passive mobilization and capsular stretching, is the mainstay of treatment for adhesive capsulitis. Physiotherapy may be counterproductive in the early painful stages of the disease. Oral and are commonly paired with physiotherapy, despite limited literature supporting a true clinical benefit to their use[62]. Distension arthrography is an invasive procedure consisting of controlled capsular insufflation to promote rupture of capsular contractures, followed by physiotherapy to preserve any improvements in motion[59]. Limited studies on arthrography indicate favorable results in primary FSS and limited efficacy in secondary disease, likely because of the need to address the underlying disease processes. Multiple case series have indicated the long-term benefits of MUA, particularly in patients with disease that is refractory to physiotherapy.

Surgical treatment options for FSS include arthroscopic and open capsular release. Arthroscopic release often is combined with MUA, which may be performed before or after arthroscopy depending on surgeon preference. The primary focus of open or arthroscopic capsular release is the debridement of contracted tissues from the rotator interval and the coracohumeral ligament. Occasionally, lengthening of the subscapularis tendon and/or posterior capsular release are required to restore internal rotation[59]. Prior studies have demonstrated favorable outcomes with both arthroscopic and open techniques[63]. Additional procedures, including subacromial bursectomy, acromioplasty, and subdeltoid debridement, also may be necessary to clear more extensive adhesions that are observed in secondary cases of FSS occurring after trauma. Open surgical release via a deltopectoral approach may be necessary in patients with disease that is refractory to arthroscopic release.

Therapeutic Outlook

AF remains a challenging problem that is encountered in many aspects of orthopaedic practice. Current treatments for AF primarily involve mechanical disruption of the pathologic adhesions and contractures via aggressive physiotherapy, physical joint manipulation, and surgical release and debridement. While there has been progress in the understanding of AF and the identification of its key biochemical mediators, effective pharmacologic treatments are lacking[64]. In recent years, newer pharmacologic treatments seeking to restore motion in patients with AF by disrupting the fibrotic cascade at the molecular level have shown promise.

Some interest has involved intra-articular injections of collagenase *Clostridium histolyticum,* which has revolutionized the treatment of Dupuytren disease in the hand throughout the past decade. Prior studies have highlighted the unique similarities of Dupuytren disease and FSS[61,65].

However, limited research has focused on the intra-articular administration of collagenase for the treatment of periarticular fibrosis as concerns for cartilage injury often preclude this as a viable treatment option[66-68].

The local delivery of antifibrotic agents, primarily relaxin-2, into the affected joint has shown some success[69]. Relaxin-2 is an antifibrotic hormone that is secreted by the placenta; it acts to promote tissue laxity by inhibiting fibrogenesis and collagen overexpression[69,70]. A recent study by Blessing et al. found that multiple intra-articular injections of human relaxin-2 moderate capsular fibrosis and restore baseline shoulder range of motion in a murine model[69]. Relaxin-2 was found to reduce concentrations of type-I collagen and to inhibit myofibroblast differentiation in the presence of TGF-β1 at the biochemical level. Histologically, murine specimens that are treated with multiple injections of intra-articular relaxin-2 demonstrated normal cellular organization that resembled control specimens, without histological evidence of fibrosis or tissue contracture[69]. Treated specimens also demonstrated complete clinical recovery of limb motion comparable with controls. If such effects can be reproduced in human subjects, relaxin-2 has potential as a future pharmacologic treatment for AF.

Overview

The prevention and treatment of AF remain a challenge in multiple areas of orthopaedic practice, including, but not limited to, cruciate ligament reconstruction surgery, TKA, and osteosynthesis of periarticular fractures. Periarticular fibrosis and scar-tissue formation restrict joint motion, leading to difficulties in patient function. At present, treatment options for AF are limited to physiotherapy and operative manipulation or debridement. Recent research involving intra-articular antifibrotic agents may offer the promise of an effective pharmacologic treatment option for AF in the future.

Ishaq O. Ibrahim, MD[1],
Ara Nazarian, PhD[2,3,4],
Edward K. Rodriguez, MD, PhD[2,3]

[1]Harvard Combined Orthopaedic Residency Program, Massachusetts General Hospital, Boston, Massachusetts

[2]Harvard Medical School Orthopedic Trauma Initiative, Boston, Massachusetts

[3]Center for Advanced Orthopaedic Studies (A.N.), and Orthopaedic Trauma Service (E.K.R.), Carl J. Shapiro Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts

[4]Department of Orthopaedic Surgery, Yerevan State Medical University, Yerevan, Armenia

ORCID iD for I.O. Ibrahim: 0000-0003-0378-1503
ORCID iD for A. Nazarian: 0000-0003-3992-3489
ORCID iD for E.K. Rodriguez: 0000-0002-8217-0593

References

1. Usher KM, Zhu S, Mavropalias G, Carrino JA, Zhao J, Xu J. Pathological mechanisms and therapeutic outlooks for arthrofibrosis. Bone Res. 2019 Mar 26;7:9.

2. Ekhtiari S, Horner NS, de Sa D, Simunovic N, Hirschmann MT, Ogilvie R, Berardelli RL, Whelan DB, Ayeni OR. Arthrofibrosis after ACL reconstruction is best treated in a step-wise approach with early recognition and intervention: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2017 Dec; 25(12):3929-37. Epub 2017 Mar 4.

3. McAlister I, Sems SA. Arthrofibrosis after periarticular fracture fixation. Orthop Clin North Am. 2016 Apr;47(2):345-55.

4. Cheuy VA, Foran JRH, Paxton RJ, Bade MJ, Zeni JA, Stevens-Lapsley JE. Arthrofibrosis associated with total knee arthroplasty. J Arthroplasty. 2017 Aug;32(8):2604-11. Epub 2017 Feb 14.

5. Ruppert M, Theiss C, Knöß P, Kendoff D, Krukemeyer MG, Schröder N, Brand-Saberi B, Gehrke T, Krenn V. Histopathological, immunohistochemical criteria and confocal laser-scanning data of arthrofibrosis. Pathol Res Pract. 2013 Nov;209(11):681-8. Epub 2013 Jul 17.

6. Mayr HO, Fassbender FF, Prall WC, Haasters F, Bernstein A, Stoehr A. Immunohistochemical examination in arthrofibrosis of the knee joint. Arch Orthop Trauma Surg. 2019 Mar;139(3): 383-91. Epub 2019 Jan 17.

7. Clark DA, Coker R. Transforming growth factor-beta (TGF-beta). Int J Biochem Cell Biol. 1998 Mar;30(3):293-8.

8. Hold GL, Untiveros P, Saunders KA, El-Omar EM. Role of host genetics in fibrosis. Fibrogenesis Tissue Repair. 2009 Dec 4;2(1):6.

9. Zeichen J, Haeder L, Jagodzinski M, Lobenhoffer P, Bosch U, Brand J. [Localisation of TGF-beta and PDGF and their relevance for the pathogenesis of arthrofibrosis]. Unfallchirurg. 2008 Feb;111(2):79-84. German.

10. Pfitzner T, Röhner E, Krenn V, Perka C, Matziolis G. BMP-2 dependent increase of soft tissue density in arthrofibrotic TKA. Open Orthop J. 2012;6:199-203. Epub 2012 May 16.

11. Magit D, Wolff A, Sutton K, Medvecky MJ. Arthrofibrosis of the knee. J Am Acad Orthop Surg. 2007 Nov;15(11):682-94.

12. Noyes FR, Berrios-Torres S, Barber-Westin SD, Heckmann TP. Prevention of permanent arthrofibrosis after anterior cruciate ligament reconstruction alone or combined with associated procedures: a prospective study in 443 knees. Knee Surg Sports Traumatol Arthrosc. 2000;8(4):196-206.

13. Shapiro MS, Freedman EL. Allograft reconstruction of the anterior and posterior cruciate ligaments after traumatic knee dislocation. Am J Sports Med. 1995 Sep-Oct; 23(5):580-7.

14. Asano T, Akagi M, Tanaka K, Tamura J, Nakamura T. In vivo three-dimensional knee kinematics using a biplanar image-matching technique. Clin Orthop Relat Res. 2001 Jul;388:157-66.

15. Kim HY, Kim KJ, Yang DS, Jeung SW, Choi HG, Choy WS. Screw-home movement of the tibiofemoral joint during normal gait: three-dimensional analysis. Clin Orthop Surg. 2015 Sep;7(3):303-9. Epub 2015 Aug 13.

16. Perry J, Antonelli D, Ford W. Analysis of knee-joint forces during flexed-knee stance. J Bone Joint Surg Am. 1975 Oct;57(7):961-7.

17. Yaru NC, Daniel DM, Penner D. The effect of tibial attachment site on graft impingement in an anterior cruciate ligament reconstruction. Am J Sports Med. 1992 Mar-Apr;20(2):217-20.

18. Romano VM, Graf BK, Keene JS, Lange RH. Anterior cruciate ligament reconstruction. The effect of tibial tunnel placement on range of motion. Am J Sports Med. 1993 May-Jun;21(3):415-8.

19. Shelbourne KD, Patel DV, Martini DJ. Classification and management of arthrofibrosis of the knee after anterior cruciate ligament reconstruction. Am J Sports Med. 1996 Nov-Dec;24(6):857-62.

20. Herbst E, Hoser C, Gföller P, Hepperger C, Abermann E, Neumayer K, Musahl V, Fink C. Impact of surgical timing on the outcome of anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2017 Feb;25(2): 569-77. Epub 2016 Aug 22.

21. Lee YS, Lee OS, Lee SH, Hui TS. Effect of the timing of anterior cruciate ligament reconstruction on clinical and stability outcomes: a systematic review and meta-analysis. Arthroscopy. 2018 Feb;34(2):592-602. Epub 2017 Sep 30.

22. Evans S, Shaginaw J, Bartolozzi A. ACL reconstruction - it's all about timing. Int J Sports Phys Ther. 2014 Apr;9(2):268-73.

23. Kim YM, Joo YB. Prognostic factors of arthroscopic adhesiolysis for arthrofibrosis of the knee. Knee Surg Relat Res. 2013 Dec;25(4): 202-6. Epub 2013 Nov 29.

24. Huleatt J, Gottschalk M, Fraser K, Boden A, Dalwadi P, Xerogeanes J, Hammond K. Risk factors for manipulation under anesthesia and/or lysis of adhesions after anterior cruciate ligament reconstruction. Orthop J Sports Med. 2018 Sep 10;6(9):2325967118794490.

25. Strum GM, Friedman MJ, Fox JM, Ferkel RD, Dorey FH, Del Pizzo W, Snyder SJ. Acute anterior cruciate ligament reconstruction. Analysis of

complications. Clin Orthop Relat Res. 1990 Apr; 253:184-9.

26. Aglietti P, Buzzi R, De Felice R, Paolini G, Zaccherotti G. Results of surgical treatment of arthrofibrosis after ACL reconstruction. Knee Surg Sports Traumatol Arthrosc. 1995;3(2):83-8.

27. Jackson DW, Schaefer RK. Cyclops syndrome: loss of extension following intra-articular anterior cruciate ligament reconstruction. Arthroscopy. 1990;6(3):171-8.

28. Bodendorfer BM, Keeling LE, Michaelson EM, Shu HT, Apseloff NA, Spratt JD, Malone PS, Argintar EH. Predictors of knee arthrofibrosis and outcomes after arthroscopic lysis of adhesions following ligamentous reconstruction: a retrospective case-control study with over two years' average follow-up. J Knee Surg. 2019 Jun;32(6):536-43. Epub 2018 May 31.

29. Stephenson JJ, Quimbo RA, Gu T. Knee-attributable medical costs and risk of re-surgery among patients utilizing non-surgical treatment options for knee arthrofibrosis in a managed care population. Curr Med Res Opin. 2010 May;26(5):1109-18.

30. Manrique J, Gomez MM, Parvizi J. Stiffness after total knee arthroplasty. J Knee Surg. 2015 Apr;28(2):119-26. Epub 2014 Dec 16.

31. Kornuijt A, Das D, Sijbesma T, de Vries L, van der Weegen W. Manipulation under anesthesia following total knee arthroplasty: a comprehensive review of literature. Musculoskelet Surg. 2018 Dec;102(3):223-30. Epub 2018 Mar 15.

32. Williams FM, Kalson NS, Fabiane SM, Mann DA, Deehan DJ. Joint stiffness is heritable and associated with fibrotic conditions and joint replacement. PLoS One. 2015 Jul 21;10(7): e0133629.

33. Awad MR, El-Gamel A, Hasleton P, Turner DM, Sinnott PJ, Hutchinson IV. Genotypic variation in the transforming growth factor-beta1 gene: association with transforming growth factor-beta1 production, fibrotic lung disease, and graft fibrosis after lung transplantation. Transplantation. 1998 Oct 27;66(8): 1014-20.

34. Gewaltig J, Mangasser-Stephan K, Gartung C, Biesterfeld S, Gressner AM. Association of polymorphisms of the transforming growth factor-beta1 gene with the rate of progression of HCV-induced liver fibrosis. Clin Chim Acta. 2002 Feb;316(1-2):83-94.

35. Jahic D, Omerovic D, Tanovic AT, Dzankovic F, Campara MT. The effect of prehabilitation on postoperative outcome in patients following primary total knee arthroplasty. Med Arch. 2018 Dec;72(6):439-43.

36. Matassi F, Duerinckx J, Vandenneucker H, Bellemans J. Range of motion after total knee arthroplasty: the effect of a preoperative home exercise program. Knee Surg Sports Traumatol Arthrosc. 2014 Mar;22(3):703-9. Epub 2012 Dec 28.

37. Schiavone Panni A, Cerciello S, Vasso M, Tartarone M. Stiffness in total knee arthroplasty. J Orthop Traumatol. 2009 Sep;10(3):111-8. Epub 2009 Jul 7.

38. Esler CN, Lock K, Harper WM, Gregg PJ. Manipulation of total knee replacements. Is the flexion gained retained? J Bone Joint Surg Br. 1999 Jan;81(1):27-9.

39. Issa K, Banerjee S, Kester MA, Khanuja HS, Delanois RE, Mont MA. The effect of timing of manipulation under anesthesia to improve range of motion and functional outcomes following total knee arthroplasty. J Bone Joint Surg Am. 2014 Aug 20;96(16):1349-57.

40. Pivec R, Issa K, Kester M, Harwin SF, Mont MA. Long-term outcomes of MUA for stiffness in primary TKA. J Knee Surg. 2013 Dec;26(6): 405-10. Epub 2013 Mar 19.

41. Desai AS, Karmegam A, Dramis A, Board TN, Raut V. Manipulation for stiffness following total knee arthroplasty: when and how often to do it? Eur J Orthop Surg Traumatol. 2014 Oct;24(7): 1291-5. Epub 2013 Dec 11.

42. Sodhi N, Yao B, Anis HK, Khlopas A, Sultan AA, Newman JM, Mont MA. Patient satisfaction and outcomes of static progressive stretch bracing: a 10-year prospective analysis. Ann Transl Med. 2019 Feb;7(4):67.

43. Aspinall S, Fong D, Godsiff S. A feasibility study considering the use of a new medical stretching device (STAK Tool) in 19 patients with knee arthrofibrosis, following total knee replacement, being considered for manipulation under anaesthetic. Presented as a poster exhibit at the 12th Biennial ISAKOS Congress; 2019 May 12-16; Cancun, Mexico. Poster no. 902.

44. Schwarzkopf R, William A, Deering RM, Fitz W. Arthroscopic lysis of adhesions for stiff total knee arthroplasty. Orthopedics. 2013 Dec; 36(12):e1544-8.

45. Tjoumakaris FP, Tucker BC, Post Z, Pepe MD, Orozco F, Ong AC. Arthroscopic lysis of adhesions for the stiff total knee: results after failed manipulation. Orthopedics. 2014 May; 37(5):e482-7.

46. Vun SH, Shields DW, Sen A, Shareef S, Sinha S, Campbell AC. A national questionnaire survey on knee manipulation following total knee arthroplasty. J Orthop. 2015 Jun 19;12(4):193-6.

47. Babyar SR. Excessive scapular motion in individuals recovering from painful and stiff shoulders: causes and treatment strategies. Phys Ther. 1996 Mar;76(3):226-38; discussion 239-47.

48. Rundquist PJ. Alterations in scapular kinematics in subjects with idiopathic loss of shoulder range of motion. J Orthop Sports Phys Ther. 2007 Jan;37(1):19-25.

49. Katthagen JC, Hennecke D, Jensen G, Ellwein A, Voigt C, Lill H. Arthroscopy after locked plating of proximal humeral fractures: implant removal, capsular release, and intra-articular findings. Arthroscopy. 2014 Sep;30(9): 1061-7. Epub 2014 Jun 14.

50. Morrey BF, Askew LJ, Chao EY. A biomechanical study of normal functional elbow motion. J Bone Joint Surg Am. 1981 Jul; 63(6):872-7.

51. Chen NC, Ring D. Terrible triad injuries of the elbow. J Hand Surg Am. 2015 Nov;40(11): 2297-303. Epub 2015 Oct 1.

52. Attum B, Obremskey W. Posttraumatic elbow stiffness: a critical analysis review. JBJS Rev. 2016 Sep 6;4(9):01874474-201609000-00002.

53. Rowe PJ, Myles CM, Walker C, Nutton R. Knee joint kinematics in gait and other functional activities measured using flexible electrogoniometry: how much knee motion is sufficient for normal daily life? Gait Posture. 2000 Oct;12(2):143-55.

54. Laubenthal KN, Smidt GL, Kettelkamp DB. A quantitative analysis of knee motion during activities of daily living. Phys Ther. 1972 Jan; 52(1):34-43.

55. Ebrahimzadeh MH, Birjandinejad A, Moradi A, Fathi Choghadeh M, Rezazadeh J, Omidi-Kashani F. Clinical instability of the knee and functional differences following tibial plateau fractures versus distal femoral fractures. Trauma Mon. 2015 Feb;20(1):e21635.

56. Kugelman DN, Qatu AM, Strauss EJ, Konda SR, Egol KA. Knee stiffness after tibial plateau fractures: predictors and outcomes (OTA-41). J Orthop Trauma. 2018 Nov;32(11):e421-7.

57. Moore TJ, Harwin C, Green SA, Garland DE, Chandler RW. The results of quadricepsplasty on knee motion following femoral fractures. J Trauma. 1987 Jan;27(1):49-51.

58. Oliveira VG, D'Elia LF, Tirico LEP, Gobbi RG, Pecora JR, Camanho GL, Angelini FJ, Demange MK. Judet quadricepsplasty in the treatment of posttraumatic knee rigidity: long-term outcomes of 45 cases. J Trauma Acute Care Surg. 2012 Feb;72(2):E77-80.

59. Robinson CM, Seah KTM, Chee YH, Hindle P, Murray IR. Frozen shoulder. J Bone Joint Surg Br. 2012 Jan;94(1):1-9.

60. Bunker TD, Reilly J, Baird KS, Hamblen DL. Expression of growth factors, cytokines and matrix metalloproteinases in frozen shoulder. J Bone Joint Surg Br. 2000 Jul;82(5):768-73.

61. Smith SP, Devaraj VS, Bunker TD. The association between frozen shoulder and Dupuytren's disease. J Shoulder Elbow Surg. 2001 Mar-Apr;10(2):149-51.

62. Wang W, Shi M, Zhou C, Shi Z, Cai X, Lin T, Yan S. Effectiveness of corticosteroid injections in adhesive capsulitis of shoulder: a meta-analysis. Medicine (Baltimore). 2017 Jul;96(28): e7529.

63. Berghs BM, Sole-Molins X, Bunker TD. Arthroscopic release of adhesive capsulitis. J Shoulder Elbow Surg. 2004 Mar-Apr;13(2): 180-5.

64. Zhang D, Nazarian A, Rodriguez EK. Post-traumatic elbow stiffness: pathogenesis and current treatments. Shoulder Elbow. 2020 Feb; 12(1):38-45. Epub 2018 Aug 8.

65. Bunker TD, Anthony PP. The pathology of frozen shoulder. A Dupuytren-like disease. J Bone Joint Surg Br. 1995 Sep;77(5):677-83.

66. Kikuchi T, Sakuta T, Yamaguchi T. Intra-articular injection of collagenase induces experimental osteoarthritis in mature rabbits. Osteoarthritis Cartilage. 1998 May;6(3):177-86.

67. van der Kraan PM, Vitters EL, van Beuningen HM, van de Putte LB, van den Berg WB. Degenerative knee joint lesions in mice after a single intra-articular collagenase injection. A new model of osteoarthritis. J Exp Pathol (Oxford). 1990 Feb;71(1):19-31.

68. Wong K, Trudel G, Laneuville O. Intra-articular collagenase injection increases range of motion in a rat knee flexion contracture model. Drug Des Devel Ther. 2017 Dec 21;12: 15-24.

69. Blessing WA, Okajima SM, Cubria MB, Villa-Camacho JC, Perez-Viloria M, Williamson PM, Sabogal AN, Suarez S, Ang LH, White S, Flynn E, Rodriguez EK, Grinstaff MW, Nazarian A. Intraarticular injection of relaxin-2 alleviates shoulder arthrofibrosis. Proc Natl Acad Sci U S A. 2019 Jun 18;116(25):12183-92. Epub 2019 Jun 3.

70. Dehghan F, Soori R, Dehghan P, Gholami K, Muniandy S, Azarbayjani MA, Yusof A. Changes in knee laxity and relaxin receptor isoforms expression (RXFP1/RXFP2) in the knee throughout estrous cycle phases in rodents. PLoS One. 2016 Aug 11;11(8):e0160984.