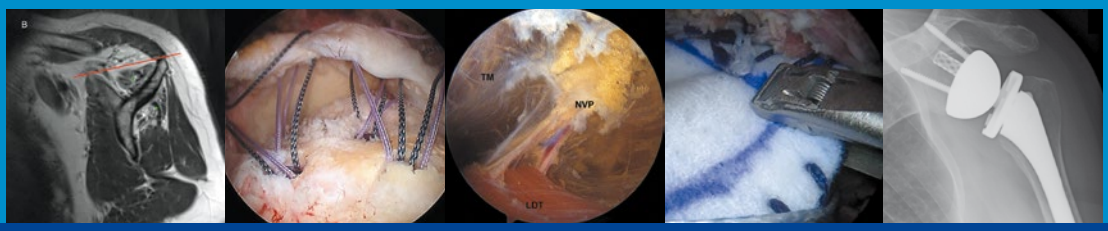
Nuno Sampaio Gomes · Ladislav Kovačič
Frank Martetschläger · Giuseppe Milano
Editors



Massive and Irreparable Rotator Cuff Tears

From Basic Science to Advanced Treatments

European Society of Sports Traumatology, Knee Surgery & Arthroscopy
ESSKA

Springer

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“To my two sons, André and Simão.” (NG)

“To my dear Eva. Thank you for your endless love and dedication to our family. Sharing the path of life together is a wonderful, joyful, and fulfilling experience.” (LK)

“To Andrea and Aaron Julius. To my parents Alfred and Irmtrud and my sister Silke.” (FM)

“To Virginia, Edoardo and Costanza. I wish you could live the life you’ve imagined in your endless imaginary world!” (GM)

Foreword

It is a pleasure to introduce this well done and much needed text on the rotator cuff. My friends and colleagues Drs. Gomes, Kovačič, Martetschlager, and Milano are all internationally recognized experts in the management of disorders of the rotator cuff. Injuries to the shoulder are quite common, but unfortunately our patients often delay treatment until the shoulder becomes severely dysfunctional.

The severely dysfunctional shoulder is usually the result of chronic, displaced, massive rotator cuff pathology. These troubled patients have become all too common, thus requiring significant improvement in management techniques. This textbook by these excellent surgeons should help our patients by improving diagnosis, planning and surgical techniques.

In short, this represents an excellent treatise on difficult problems. I think it is a must-read for any surgeon treating chronic shoulder issues.

New Orleans, LA, USA — Felix H. "Buddy" Savoie III

Preface

As some of the readers of this book may well remember, the array of common surgical procedures performed on the shoulder at the early stages of their practice as surgeons was considerably less vast than it is today. With the advent of arthroscopy, a whole new universe of possibilities was disclosed, not only because new diagnosis and successful treatment techniques were described but also because keyhole surgery, due to its inherent appeal, seduced many of us to eagerly contribute to its development over the past years.

Scientific knowledge of the shoulder joint is, therefore, profound these days. The European Shoulder Associates (ESA) of ESSKA, gathering many of the current international leading shoulder surgeons, is a good example of the dynamism and strength of the scientific and technical evolution that exists today on this matter. Its biennial meeting in 2019 was, for the first time, organized as a joint event with the other sections of ESSKA—the Speciality Days—in a brand new format that proved to be a success. Especially for ESA, awarded the Best Section Performance prize of the meeting! It was held in Madrid on November 2019, focusing on a topic that continues to impel many shoulder surgeons towards the best possible solutions for a frequent shoulder problem, the massive rotator cuff tear.

The scientific chairs are proud to present this monograph, based on the same theme they explored at the Speciality Days. Besides the contribution of the meeting participants, other related topics are also covered in this book that include the role of both conservative and surgical management, from new biological options to all potential surgical techniques. In addition, the value of anesthesia and regional blocks, as well as guidance on the management of treatment complications and failures, are also included.

We are thankful to the ESSKA Board for supporting this project and to Springer for their high professionalism.

Porto, Portugal — Nuno Sampaio Gomes

Contents

Part I

Basic Science

Massive and Irreparable Rotator Cuff Tears: Defining the Problem

1

Lukas N. Muench, Felix Dyrna, and Knut Beitzel

1.1 Introduction

Massive and irreparable rotator cuff tears remain a major challenge in shoulder surgery [1]. Due to pain, loss of range of motion, and insufficient function, these tears significantly affect the patients' quality of daily living [1]. Representing up to 40% of all rotator cuff tears, massive tears are associated with persistent defects and poorer clinical outcomes [2, 3]. Imbalance of the force couples results in unstable kinematics of the glenohumeral joint, causing the remaining shoulder function to be sustained by a significantly increased compensatory deltoid force [4, 5].

This article tries to provide a structured overview about the biological challenges and biomechanical consequences of massive irreparable rotator cuff tears, as understanding of these factors is essential to initiate a differentiated therapeutic approach. Beginning with the different existing classification systems as well as initiation and progression of massive rotator cuff tears, the authors try to outline successively the biological problems including healing potential and tissue degeneration, followed by the main biomechanical problems. These mainly comprise the effects on tractive forces, shoulder function, glenohumeral joint centering and the development of osteoarthritis. In clinical practice, all of these factors have to be considered, in order to achieve satisfactory improvement in functional outcomes.

1.2 Structural Problem

1.2.1 Classifications of Massive Rotator Cuff Tears

Massive rotator cuff tears can be characterized by size, chronicity, and location. Regarding the tear size, different definitions exist. DeOrio and Cofield [6] defined massive tears as those whose greatest diameter exceeds 5 cm. Contrarily, Gerber et al. [7] characterized massive tears as those including complete tears of at least two tendons. This definition may show a more consistent correlation to the patients' function, prognosis, and outcome [5, 7, 8]. Considering chronicity, massive tears can be classified as acute, acute-on-chronic, and chronic tears [5]. Acute tears are relatively rare, commonly occurring

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after a traumatic event in younger patients [5]. In contrast, chronic massive tears are mostly observed in the elderly [5]. Regarding location, massive tears mostly follow the two distinct patterns of anterosuperior and posterosuperior tears [5].

1.2.2 Tear Initiation and Progression

Previous studies have proposed that degenerative rotator cuff tears start with the supraspinatus tendon, typically initiating at the anterior part of the humeral insertion near the biceps tendon, and propagate posteriorly over time [9–12]. In contrast, more recent studies have found that full-thickness as well as partial-thickness rotator cuff tears most commonly initiate at a location approximately 10–15 mm posterior to the biceps tendon, and may even begin with the infraspinatus tendon [10, 11, 13, 14]. An explanation for this finding is based on the "rotator crescent" concept, first described by Burkhart et al. [11, 15]. The rotator crescent is a term describing the thin, crescent-shaped rotator cuff sheet, which spans from the biceps tendon to the inferior border of the infraspinatus tendon, and is bound proximally by an arch-shaped thick bundle of fibres, called the "rotator cable" [15]. The rotator cable preserves the rotator crescent from stress through a "suspension bridge" configuration [15].

As people age, relative avascularity may lead to progressive thinning of the crescent, thus increasing dependence on the rotator cable [11, 15]. The location found by Kim et al. [11] 15 mm posterior to the biceps tendon is approximately at the center of the rotator crescent [15]. However, a recent MRI study located the initial tear site 5 mm more anterior (9–10 mm posterior to the biceps tendon) than as described by Kim et al. [10, 11]. This leads to the assumption that tears might propagate in both anterior and posterior directions [10]. Given the fact that the supraspinatus footprint is much smaller than previously believed, this location may be regarded as either the junction between the supraspinatus and infraspinatus, or being purely within the infraspinatus tendon [11, 16].

As torn tendons cannot participate in load distribution, the increasing tensile load on the remaining fibres can easily lead to tear propagation, particularly if the remaining tendon is of poor quality [17].

1.3 Biological Problem

1.3.1 Healing

The tear size can directly affect the clinical outcome and tendon healing [18–20]. A series of arthroscopic rotator cuff repairs have demonstrated that postoperative healing usually occurs between 71 and 89% of cases [19, 20]. However, this rate of tendon healing may drop to 47 or 50% in the treatment of massive rotator cuff tears [19, 20]. Even though hypovascularity has been hypothesized to facilitate tear initiation and limit biological healing after repair, the complexity of the healing process has not been fully understood [21].

The cells contributing to natural tendon healing originate from loose connective tissue surrounding the tendon fascicles and tendon body [22]. In response to the injury, these cells proliferate and migrate toward the tear site where they form collagenous healing tissue [22–24]. As the endogenous healing potential of the tendon seems to be limited, biologic augmentation techniques have recently garnered more and more attention, including the application of growth factors, platelet concentrates, or mesenchymal stem cells (MSCs) [25, 26]. Despite bone marrow being the traditional source for MSCs for biologic augmentation of tendon injuries, recent studies have highlighted subacromial bursal tissue being a source of MSCs, demonstrating superior proliferation potential, tissue engraftment, and survival [22, 26–29].

1.3.2 Atrophy, Fatty Infiltration, Retraction, and Loss of Elasticity

In addition to tear propagation, the process of atrophy, fibrosis, and fatty infiltration may occur in the rotator cuff tendon, as well as in the associated muscle belly over time (Fig. 1.1) [7, 20,

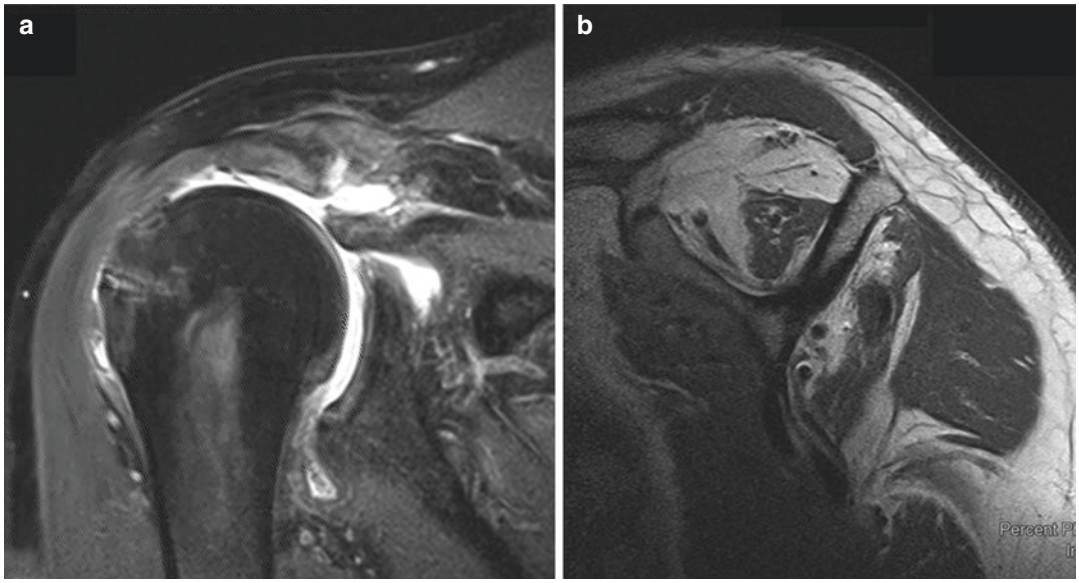

Fig. 1.1 MRI scan demonstrating a massive re-tear of the rotator cuff tendons with retraction, atrophy, and fatty infiltration. (**a**) Coronal view and (**b**) sagittal view

30]. Moreover, these tears often cause the tissue to become less compliant and stiffer [20, 30]. Particularly, in combination with tissue atrophy or fatty infiltration, this may result in severe tendon retraction [20, 30]. A widely retracted tendon margin coupled with poor tissue quality makes surgical mobilization difficult and sometimes impossible (Fig. 1.2) [20].

Muscle atrophy and fatty infiltration have been reported to be independent factors predicting outcomes and success rate after rotator cuff repair [31]. As tears of the rotator cuff result in mechanical unloading and denervation due to suprascapular nerve injury, consistent pathological changes can occur in the muscles' myotubes [32–34]. This may lead to alterations in the central molecular pathways, which regulate muscle atrophy and hypertrophy through mechanical load signaling [32–34].

A cell subpopulation of interstitial pluripotent stem cells, named fibro-adipo-progenitor cells (FAPs) and resident in muscle tissue, has been identified to be the cellular source of fatty infiltration [35, 36]. As shown in a mouse model, FAPs proliferate and differentiate into cells primarily expressing fat genes and cellular markers of adipogenesis, after inducing cuff injury [35, 36].

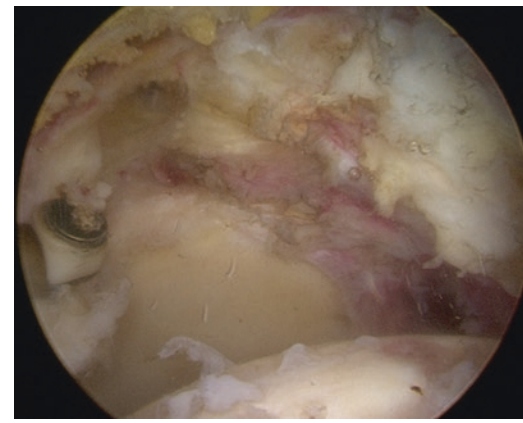

Fig. 1.2 Arthroscopic view of a large, retracted massive rotator cuff tear with concomitant tissue degeneration

Large, retracted tears have also been shown to cause traction on the suprascapular nerve, and may contribute to the progression of atrophy and fatty infiltration of the supraspinatus and infraspinatus muscles [17]. Moreover, the tear initiation location found by Kim et al. [11] may explain why fatty degeneration of the infraspinatus is seen in some patients with a presumed isolated tear of the supraspinatus tendon, highlighting the need to assess its integrity.

1.4 Biomechanical Problem

1.4.1 Tractive Forces

Coordinated action between the rotator cuff and deltoid muscles is essential for a sufficient glenohumeral abduction motion [37]. As the anterior and middle deltoid show preferential muscle activity and loading from 30° to 90° of glenohumeral abduction, the supraspinatus is the dominant muscle during the first 30°, and therefore the main initiator of abduction [37, 38]. Rotator cuff tears may lead to kinematic alterations, potentially causing a significant change in the biomechanical synergy between deltoid and rotator cuff muscles [39]. As the cuff tear size propagates posteriorly, considerably greater amounts of force are placed upon the middle portion of the deltoid, showing a major increase between 10° and 45° of abduction [4, 40, 41]. At the same time, the mechanical advantage of the deltoid may be disrupted due to loss of balanced concavity-compression and superior translation caused by tear progression [4]. This results in greater forces required to maintain joint stability and decreased abduction capability [4, 41, 42].

A recent biomechanical study highlighted the required compensatory deltoid function to compensate for abduction motion loss in the presence of simulated rotator cuff tears [4]. Anterosuperior (combined supraspinatus and subscapularis) tears resulted in the largest loss in glenohumeral abduction motion, despite the greatest increase in deltoid force [4]. On the other hand, isolated subscapularis tears increased the anterior deltoid force, compensating for the loss of anterior joint compression without a reduction in abduction [4].

1.4.2 Shoulder Function and Pseudoparalysis

The rotator cuff muscles are important contributors to a smooth glenohumeral motion and sufficient joint stability [17]. Acting as force couples, they collaborate to stabilize the inherently unstable glenohumeral joint [17]. The deltoid and the inferior portion of the rotator cuff act as the coronal force couple, compressing the humeral head to the glenoid in abduction [43]. Subscapularis and infraspinatus/teres minor represent the axial force couple, providing a fulcrum for the actions of the deltoid and supraspinatus, which is essential to maintain joint stability by a compressive joint reaction force in the axial plane [17, 37, 43].

Massive rotator cuff tears may disrupt these force couples resulting in superior migration of the humeral head and dysfunction of the shoulder (Fig. 1.3) [5, 17]. The importance of the force couples was highlighted by introducing the "suspension bridge" concept [43]. Accordingly, shoulder function may be maintained in isolated supraspinatus tears due to intact force couples [43]. However, as tears propagate into the anterior or posterior cuff direction, force coupling is disturbed, resulting in unstable kinematics and loss of function [43].

In addition, instability of the glenohumeral joint results in increased internal rotation in the setting of posterosuperior tears, external rotation in anterosuperior tears, and the total rotational range of motion in all abduction angles [44]. To maintain normal kinematics in the presence of massive cuff tears, greater forces by both the deltoid and the corresponding force couple muscle

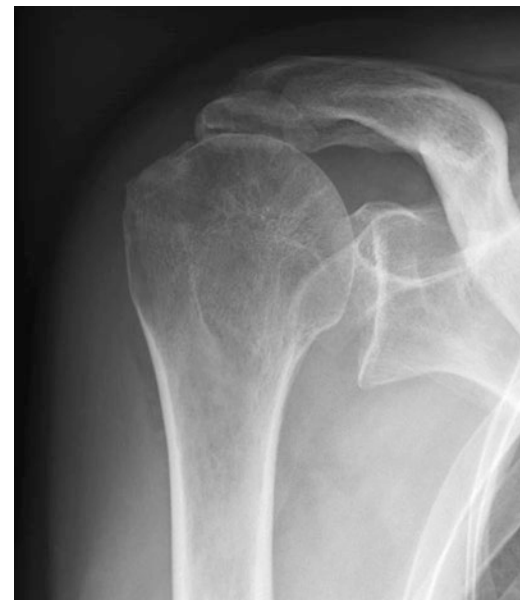

Fig. 1.3 X-ray demonstrating the superior migration of the humeral head

are required to achieve a coordinated abduction motion [4, 40].

Due to these kinematic changes, pseudoparalysis of the shoulder may occur (Fig. 1.4). The most common definition is active elevation less than 90° with full passive elevation [1, 45–47]. Risk factors are considered to be disruption of the entire subscapularis or of the three rotator cuff muscles [45]. However, recently it has been reported that pseudoparalysis should rather be described as no active elevation with maintained passive elevation of chronic nature, usually with anterior–superior escape and being refractory following an injection [1]. This definition may be more adequate, as pseudoparalysis is often confused with pain [1]. Therefore, pain should be ruled out as a cause of apparent pseudoparalysis, since patients may benefit from a pain-relieving treatment alone [1]. Sometimes, an injection of lidocaine for pain elimination will clarify the diagnosis in the face of a massive rotator cuff tear [1].

1.4.3 Decentralization, Glenohumeral Joint Pressure, and Osteoarthritis

Sufficient function of the rotator cuff muscles is essential to ensure glenohumeral stability through the concavity compression principle [48, 49]. Loss of rotator cuff integrity may significantly alter the joint-reaction forces, which are required to maintain glenohumeral stability [48, 49]. Dysfunction of the infraspinatus and subscapularis may lead to superior humeral head translation and joint instability by displacing the glenoidal contact point superiorly [4, 41].

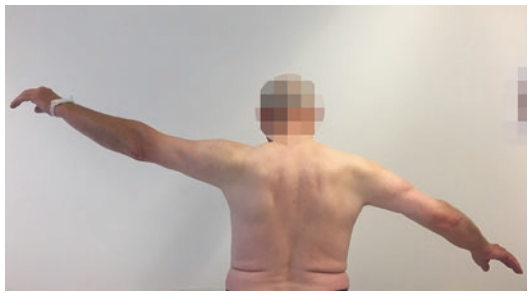

Fig. 1.4 Patient with severe pseudoparalysis of the right cuff-deficient shoulder

The abnormal joint loading due to rotator cuff insufficiency may cause various erosion patterns, frequently seen in type B glenoids of osteoarthritic patients [50, 51]. Recent literature suggests that this wear pattern is not axisymmetric to the superoinferior axis of the glenoid, but rather orientated in the posteroinferior region [50, 51]. Over time, these erosion patterns may lead to significant glenoid bone loss, presenting a major challenge in reverse shoulder arthroplasty [50–52]. However, three-dimensional reconstruction has allowed further analysis of glenoid erosion patterns. This is much needed, since the two-dimensional CT images inaccurately represent the wear pattern in osteoarthritic glenoids [51]. Unfortunately, it still remains uncertain if osteoarthritis results in altered kinematics and subluxation, or if the changed kinematics with subluxation is instigating this inflammatory disease [51].

Finally, massive cuff tears may lead to cuff tear arthropathy (CTA), which is defined as muscle degeneration, including fatty infiltration and atrophy, along with bony alterations, such as humeral head erosion and acetabularization of the acromion [53]. The underlying pathway may be induced by a massive cuff tear with anterosuperior escape, followed by a mechanical conflict between the humeral head and the superior glenoid and acromion [54]. In addition to the collapse of cartilage and bony structures, enzymes may be released that impair the surrounding tissue, thus leading to pain and limited shoulder function [53]. Maintenance of a sufficient rotator cuff function has been shown to be vital to delay the development of glenohumeral arthritis, highlighting the necessity of a good repair technique [55]. However, in the presence of severe CTA, these repair techniques may be infeasible, calling for reverse total shoulder arthroplasty instead.

1.5 Conclusion

Due to the combination of impaired biological healing potential and joint affecting biomechanical changes, massive irreparable rotator cuff tears

Table 1.1 Key factors

Nature of the problem	Key factors
Structural	• Most massive tears follow distinct patterns (antero- and posterosuperior) • Progressive thinning of the rotator crescent facilitates tear initiation • Increased tensile load on remaining fibres leads to tear progression in both anterior and posterior directions
Biological	• Hypovascularity limits biological healing potential • Tissue degeneration includes atrophy, fatty infiltration, retraction, and loss of elasticity making surgical repair difficult
Biomechanical	• Mechanical advantage of the deltoid muscle is comprised of higher tractive forces and loss of balanced concavity-compression • Disruption of force couples leads to superior humeral head migration and shoulder dysfunction (pseudoparalysis) • Glenohumeral instability causes humeral head decentralization • Glenoidal erosion patterns may progress to severe CTA

remain a major challenge in shoulder surgery. For the treatment of these patients and defining the underlying problems (Table 1.1), the interaction of biological and biomechanical pathomechanisms has to be considered. As biological healing may be impaired by hypovascularity as well as tissue degeneration including atrophy, fatty infiltration, and tendon retraction, concomitant biomechanical alterations of glenohumeral joint kinematics may result in shoulder dysfunction and lead to the development of cuff tear arthropathy in the long term.

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Biology of Rotator Cuff Injury and Repair

2

Alessio Giai Via, Davide Cucchi, and Laura de Girolamo

2.1 Histological Features

2.1.1 The Normal Tendon Tissue

Tendons are the anatomical structures responsible for the transmission of forces from muscles to bones, and thus are crucial in allowing joint movement [1]. They are mainly made of collagen type I molecules hierarchically organized into tropocollagen (a polypeptide chain made of a triple helix, the building blocks of fibrils), which are bundled in fibers surrounded by the endotenon and eventually compose fascicles [2]. Fascicles associated together represent the tertiary bundles, which altogether constitute the tendon itself [3, 4]. A number of different collagen molecules, proteoglycans (PGs), glycosaminoglycans (GAGs) and noncollagenous proteins (tenascin, fibronectin, elastin, decorin, etc.) are responsible for this complex structural organization. While collagen provides tensile strength, the other components of tendon extracellular matrix (ECM) allow for structural support and regulate fibril and fiber assembly [4]. The epitenon, a thin membrane surrounding the tendon, provides supply to the tissue in terms of vascularization and innervation. At the outer layer, the epitenon is surrounded by the paratenon, a sheat of connective tissue made of collagen fibrils (mainly type I and III) [5].

Resident tendon cell population comprise both tenocytes, displaying an elongated shape, and tenoblasts, rounded progenitor cells [6]. These cells, embedded in tendon ECM, are responsible for the synthesis and the remodeling of the molecules composing the fibers.

The remodeling activity of these cells is important for the maintenance of tissue homeostasis and function, particularly in tendons with high functional demand, such as the supraspinatus and the Achilles tendons [7, 8], where it represents a protective mechanism against tissue damage [9]. Remodeling is also crucial in the early phases of tissue repair and healing, while failure in this process may cause the formation of scar tissue, thus compromising the mechanical properties of tendons [10]. Matrix Metalloproteinase-1 (MMP-1) is the main enzyme involved in collagen type I degradation [11] and its activity is controlled at many levels to prevent aberrant matrix disruption leading to tissue degeneration [12]. The importance of the remodeling mechanisms was

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clearly demonstrated by Millar and colleagues, who showed the correlation between MMP inhibition and the onset of painful lesions [13].

The portions of tendons towards muscle, as well as those close to the bone, are specialized regions with different ECM compositions and cellularities. In particular, in the bone-tendon junction the transition of the tissue from tendon towards bone comprises zones of fibrocartilage and mineralized fibrocartilage [14].

Upon light microscopy, the normal tendon appears as a dense tissue made of parallel collagen bundles, with a few scattered cells showing elongated nuclei. Small vessels are found in the endotenon, following a parallel orientation with respect to the collagen fibers [1, 4, 15] (Fig. 2.1a).

The supraspinatus tendon in the rotator cuff is responsible for the stabilization of the shoulder joint, and it is an example of the complex organization characterizing some tendons. Indeed, it is composed of a multilayered structure, each layer presenting a different fiber orientation [16]. Fifty-six percent of its dry weight is collagen [8], with type I and type III collagen cross-links to form each fibril [17]. The cross-link among collagen molecules is crucial to obtain the definitive tendon structure, and in the supraspinatus tendon these elements are more present with respect to the average tendon, probably due to higher functional demand in terms of shear stress and load it has to sustain [18]. For the same reason, the supraspinatus tendon contains a higher amount of proteoglycans, in particular, aggrecan and byglican [19].

2.1.2 The Pathological Tendon Tissue

Tendon pathologies are commonly classified with the term "tendinopathy," comprising a wide spectrum of conditions, from inflammation to ruptures, through different grades of tears and tissue degeneration [20]. In this condition, several modifications of tissue histopathology occur: collagen fibers separate, reducing their dimension and losing the parallel orientation, thus resulting in decreased tissue density; microtears may be observed, in the form of erythrocyte accumulation in the presence of fibrin and fibronectin deposits; increase of vascularization; infiltration of adipose tissue within the tendon (Fig. 2.1b). Moreover, tendinopathy is associated with an overall increase of collagen type III, contributing to tissue density reduction and loss of fiber orientation, and influencing the appearance of the tissue under polarized light, with reduced reflectivity if compared to the normal tissue [21]. Another characteristic of this condition is the uneven distribution of tendon cells within the tissue, with some areas containing a high cell density, where tenocytes may show a

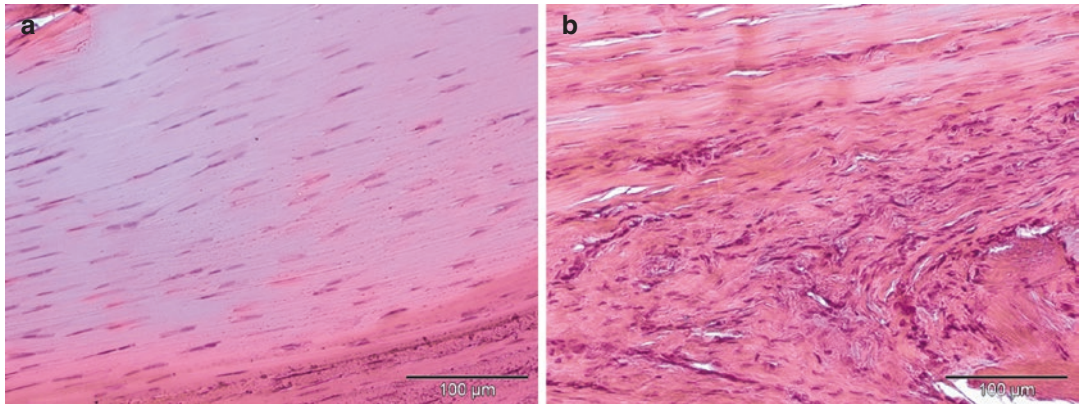

Fig. 2.1 Hematoxylin and eosin staining of tendons. (**a**) Normal tendon appearance with parallel collagen fibers and few elongated cells; (**b**) degenerated tendon tissue, with loss of fiber orientation and an increased number of cells showing a round shape. Scale bar: 100 µm

chondroid appearance, with rounded nuclei and a cytoplasm rich in PGs and GAGs, and other areas with decreased density, where a few cells have a small nuclei with an apoptotic/necrotic appearance [21, 22]. The role of inflammation in tendinopathy has been considered negligible for most of the twentieth century, but it is nowadays well recognized, thanks to the introduction of more sophisticated techniques, in particular in the field of immunohistochemistry. In fact, lymphocytes T and B and macrophages have been described in chronic Achilles tendinopathy, while granulocytes characterize the asymptomatic tendon ruptures [23]. At the same time, different markers of inflammation have been found in tendon pathological contexts, for example cyclooxygenase 2 and interleukin-1β (IL -1β) [24, 25].

As already mentioned, neovascularization is a key feature of tendinopathy, and since it is usually accompanied by innervation, it may be responsible for the symptomatic pain in tendon disorders [26].

The hierarchical structure of tendons allows for the establishment of a fail-safe mechanism, since the failure of few fibers would not affect the functionality of the whole tendon. Nevertheless, the etiology of tendinopathy is usually described as derived from the unequal distribution of load across the tendon or by repeated strain, possibly leading to fatigue failure of multiple fiber bundles and to the separation of layers within the tendon tissue [27, 28], causing overuse injury.

2.1.3 Histological Findings of Rotator Cuff Tendinopathy

As mentioned before, tendons from the rotator cuff have a complex organization and they are characterized by a higher content in PGs and GAGs as well as a higher density of cross-links among the collagen fibers, with respect to other tendons. Nevertheless, the degeneration of this tissue results in further accumulation of GAGs, especially between fibers, as well as a morphological change of tendon cells, from an elongated to rounded shape, forming fibrocartilage-like areas [29–31]. In addition, reduction in cell density, tissue calcification, neovascularization, and lipid infiltration are common features of the degenerated supraspinatus tendon that usually occur in patients over 60 years old [32]. In general, ruptured supraspinatus tendons usually show severe degeneration, in particular characterized by reduced cellularity and fiber disorganization [32]. Typical features also comprise the onset of tears and the reduction of fiber dimension. In advanced stages, cell necrosis and tissue calcification may occur [33–35]. From the biochemical point of view, the key markers of inflammation and tendon remodeling, IL-1β and MMP-1, resulted in an increase in ruptured supraspinatus tendons [24]. Nevertheless, it is still unclear whether the presence of these markers represents an acute response to rupture or if they are related to the degeneration process. On the other hand, a higher proportion of collagen type III in the tissue is an indicator of previous injuries and traumas, resulting in scar tissue with a lesser quality with respect to native tendon and thus more prone to rupture [36, 37].

2.1.4 The Role of Hypercholesterelemia in Tendinopathy

Besides traumas and overuse, hypercholesterolemia (HC), i.e., a high blood content of cholesterol (>240 mg/dL), recently emerged as a possible cause of tendon degeneration. Histological studies showed that high cholesterol levels may alter the tendon microenvironment via local changes in gene expression, protein synthesis and ECM turnover. In particular, high serum cholesterol levels allow for the accumulation of oxidized-low-density lipoproteins (LDL), which are lipids carrier proteins. Lipid accumulation within tendon ECM may affect the mechanical properties of the tissue [38, 39] correlating with a lower healing potential after surgical repair, as observed in animal models [40, 41]. Clinical studies often show conflicting results regarding the relationship between HC and tendon disorders [42, 43], but the majority of the studies investigating the correlation of

HC, hyperlipidemia or dyslipidemia and tendon pathologies demonstrated a correlation between the systemic levels of lipids and the development of tendon disorders, in particular rotator cuff disease [42, 44]. A possible explanation of the relation between body mass index (BMI) and tendinopathy could be the excessive loading on the musculoskeletal system exerted by overweight individuals. Nevertheless, this explanation is simplistic, given the molecular changes that have been observed in tendons of subject affected by hypercholesterolemia and normal tendons. Indeed, in HC condition, cholesterol deposits are found within tendon ECM and cells, with a direct influence of the mechanical properties of the tissue [40, 45]. In addition, inflammation is a direct consequence of HC, also causing cardiovascular diseases, and the infiltration of macrophages in the tendons of patients affected by HC has been observed [46]. At the same time, HC results in an alteration of matrix deposition in different tissues, affecting the synthesis of noncollagenous proteins [47], the proportion of collagen type III [48], and the production of PGs [49]. Taken together, these observations indicate that HC may significantly alter the composition of tendon ECM, explaining the reduction of the supraspinatus tendon biomechanical properties, the higher rates of tendon injury, and the decrease in tissue healing observed in animal models of HC [41, 50]. Based on these results, HC emerged as a risk factor for tendon degeneration, causing structural/mechanical modifications and fostering inflammation. Indeed, while overuse is considered the most common cause of tendinopathy, the involvement of HC would explain the onset of these disorders in the population of inactive patients with high body mass index (BMI) [51, 52].

2.2 Rotator Cuff Injury

Rotator cuff injury has a multifactorial pathogenesis, which includes anatomical, mechanical (or extrinsic), and biological (or intrinsic) factors. Many theories have been postulated to explain the pathogenesis of rotator cuff tears (RCTs), trying to unify intrinsic and extrinsic theories, but the precise role of each factor is not fully understood yet. However, recent evidence strongly suggests that most of the tendinopathies and tendon ruptures are caused by primary failed healing response [53].

2.2.1 Mechanical and Extrinsic Factors

2.2.1.1 Anatomy

Anatomic differences have been considered as a risk factor for RCTs. The critical shoulder angle (CSA) is the angle between a line connecting the inferior and superior margins of the glenoid fossa, and a line drawn from the inferior edge of the glenoid to the lateral aspect of the acromion, measured on anteroposterior plain radiographs (Fig. 2.2). Moor et al. found that a large CSA was an independent predictor for a posterosuperior RCT [54]. Gerber et al. showed that a large CSA increased the instability ratio (the ratio of join shear force to joint compression force), in particular at about 60° of abduction, and that the load on the supraspinatus tendon increased by 33% in response to the increased shoulder instability [55]. This could produce the supraspinatus tendon

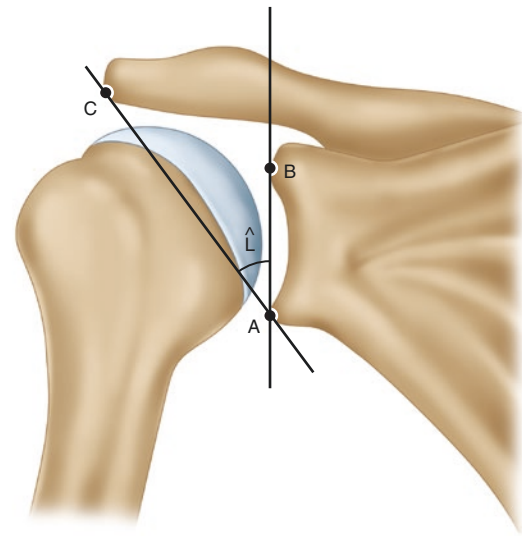

Fig. 2.2 The critical shoulder angle (CSA) is the angle between a line connecting the inferior and superior margin of the glenoid fossa, and a line drawn from the inferior margins of the glenoid to the lateral aspect of the acromion

tear. The size of the acromion is also an additional anatomic risk factor. Nyffeler et al. demonstrated that the lateral acromion index (the distance from the lateral border of the acromion to the glenoid plane divided by the distance from the lateral border of the humeral head to the glenoid plane) was significantly larger in patients with full-thickness RCTs compared to controls [56].

Mechanical factors have been proposed to be a cause for RCTs, because the confined position of the supraspinatus tendon within the subacromial space makes this tendon more susceptible to degenerative changes. Neer and Poppen first described a subacromial impingement theory in 1972. Based on the intraoperative findings, the authors found that RCTs mainly occurred in the supraspinatus tendon, in an area that contatcted the coracoacromial ligament, the anterior acromion, and sometimes the acromion-clavicular joint during forward elevation, concluding that 95% of RCTs were caused by subacromial impingement [57]. In support of this theory, the acromial shape was classified into three types by Bigliani et al. Type II (curved) and type III (hooked) have been statistically associated with RCTs, and type III acromion has been considered responsible for about 70% of supraspinatus tendon tears [58]. A systematic review by Seitz et al. concluded that patients with full-thickness RCTs have a significantly smaller acromiohumeral space than controls. However, although the narrowing of the subacromial space has been classically associated with RCTs, it not clear whether impingement induces tendon injury or a primary rotator cuff dysfunction leads to subacromial impingement by the resulting superior humeral translation [59]. Acromial shapes can be both congenital and acquired. Age determines the progression from a flat to a curved or hooked acromion, possibly because of traction forces. This would partially explain the epidemiological evidence of higher incidence of RCTs with increased age, but also suggests a primary intrinsic moving factor [60].

2.2.1.2 Overuse

Mechanical overuse is also involved in rotator cuff disease, as suggested by the frequent observation of symptomatic disease in the dominant arms rather than in the nondominant arms. Mechanical overuse of the supraspinatus tendon has been studied by Soslowsky et al. in a rat model [61, 62]. Tendons in the overuse model exhibited an increased cross-sectional area, hypercellularity, and collagen disorganization. Maximum stress and elastic modulus were significantly lower in the overuse group compared to control rats. However, chronic overuse injury is only one of the several factors contributing to the pathogenesis of RCTs, as 28% of patients present full-thickness tear in the nondominant arm, and 36–50% of patients have bilateral full-thickness tear, especially in older patients [63, 64].

2.2.1.3 Cigarette Smoking

The other extrinsic factor is cigarette smoking, which has been associated with rotator cuff injury and poorer outcomes after repair. Many studies reported that nicotine and carbon monoxide decrease microperfusion and tissue oxygenation, leading to tissue hypoxia [65]. The supraspinatus tendons in smokers showed significantly more advanced degenerative changes, with increased density of apoptotic cells, reduced tenocyte density, and down regulation of proliferative activity [66]. This relationship is dose-dependent and time-dependent [67].

2.2.2 Biological Factors

2.2.2.1 The Role of Vascular Supply

A hypovascular zone, the so-called "critical zone," has been traditionally described 10–15 mm proximal to the insertion of the supraspinatus tendon [68]. It is unclear whether this hypoperfusion contributes to tendon's degeneration, because histological and intraoperative studies showed relative hyperperfusion at this area and at the tear edge [31]. Brooks et al. showed that both the vessel diameter and their number were approximately reduced by third at 5 mm from the cuff edge compared with 30 mm, but no significant hypovascularization has been identified [69]. However, when the arm is in full adduction, the supraspinatus is compressed by the humeral head into the subacromial space, and blood perfusion may significantly be reduced.

2.2.2.2 The Role of Diabetes Mellitus

Diabetes mellitus has been associated with compromised tendon function, increased susceptibility to tendon injury, and reduced healing ability [70]. Worse results after rotator cuff repair and higher incidence of re-ruptures have been reported in diabetic patients compared to nondiabetic controls [63]. Accumulation of advanced glycation end-products (AGEs) impaired collagen production and ECM formation, and compromised angiogenesis caused by elevated glucose concentration may be suggested as a probable pathogenesis of tendinopathy in patients with diabetes mellitus. Protein glycation is a spontaneous reaction depending on the degree and duration of hyperglycemia, the half-life of protein, and permeability of the tissue to free glucose. Glycated proteins can undergo further reactions giving rise to AGEs, which are complex, heterogeneous molecules that cause protein cross-linking, and alter the physical characteristics of collagen fibers [71]. In tendons, AGEs formation affects the interactions between collagen fibers, ECM protein, and tenocytes [72]. These changes have been associated with both reduced healing capacity and altered mechanical properties of connective tissues. The effects of AGEs on the mechanical properties of tendons have been studied in a rat model [70]. The formation of AGEs would change the way tendons respond to loading, in particular reducing tissue viscoelasticity by severely limiting fibril–fibril sliding, making tendon more susceptible to injury. This has been recently confirmed by an in vitro study by Gautieri et al. [73]. Interestingly, Chung et al. found a significant overexpression of MMP-9 and IL-6 genes in the torn supraspinatus tendon of diabetic patients compared to controls, concluding that the increased MMP-9 and IL-6 synthesis might significantly compromise the integrity of tendon ECM and predispose patients with diabetes to tendinopathy or rupture [74].

2.2.2.3 The Role of Thyroid Hormones

The relationship between thyroid disorders and shoulder pain has been suspected since the late 1920s [75]. More recently, such association has been formally hypothesized. A recent epidemiological study by Oliva et al. showed that nearly 60% of patients that received arthroscopic rotator cuff repair were also affected by thyroid disorders [76]. The influence of thyroid hormones on the pathogenesis of tendinopathy has been confirmed by an in vitro study that showed the presence of thyroid hormones receptors on tenocytes. Thyroid hormones were able to induce tenocyte growth, to reduce the doubling time, and they also counteracted apoptosis in a dose- and time-dependent manner. Thyroid hormones are also able to influence tenocyte secretion of ECM proteins [77]. When tenocytes have been cultivated in the presence of T3 or T4 individually or in combination with ascorbic acid, thyroid hormones significantly increase the expression of collagen type I. Furthermore, the synthesis of cartilage oligomeric matrix protein (COMP) was also increased. COMP is a glycoprotein that binds collagen type I, II, and IX and fibronectin, and it is largely present in tendon exposed to compressive load. All these data confirm the essential role of thyroid hormones in regulating tenocytes' proliferation and ECM homeostasis [78].

2.2.2.4 The Role of Cholesterol and Lipids

As already reported (2.1.4), hypercholesterolemia has been implicated as a risk factor for tendinopathy, including rotator cuff injury [79, 80].

High serum cholesterol levels allow for the accumulation of oxidized-low-density lipoproteins (LDLs), which are lipid carrier proteins [43]. The clinical manifestation of LDL accumulation in human tendons is xanthoma, which is the major tendon disorder in patients with familial dyslipidemias. Lipids found within xanthomas derive from the circulating plasma rather than being synthesized locally [81].

2.2.3 Genetic Factors

2.2.3.1 The Role of Apoptosis

Recent studies suggested the contribution of genetic factors in the pathogenesis of RCTs. Many authors described the increased risk of

experiencing symptoms (five times) and of developing RCT (more than twice) among siblings and second-degree relatives [82–84]. Even if the exact genetic profile is still under investigation, some genes responsible for being more susceptible to RCT have been described.

Animal studies showed a higher gene expression of glutamate, and high levels of intratendinous glutamate have been revealed in a rat model of supraspinatus tendon tear [85]. Glutamate is a neurotrasmitter of the central nervous system, and high extracellular glutamate concentration has been related with neurodegenerative disorders such as Huntington and Alzheimer diseases, and seems to be deleterious for cells ("excitotoxicity") [86]. Interestingly, glutamate cascade has been related to functional adaptation of bone to mechanical loading, and in vitro study showed that it has a pro-apoptotic effect in cultured tendon fibroblasts, by regulating the expression of apoptosis-related genes [87, 88]. Therefore, even if the exact significance of high glutamate synthesis is not completely understood, the gene-expression may be related to rotator cuff tears.

Recent studies pointed out that apoptosis plays a key role in the pathogenesis of tendon injury [89]. Apoptosis is a highly regulated cellular process involved in the development of multicellular organisms, and because of its role in the control of cell population, it is essential for the homeostasis of adult tissues. Excessive apoptosis within the rotator cuff tendon can alter the balance of normal tissue turnover, and promote increased tendon degradation. Yuan et al. showed an increased prevalence of apoptotic tissue within the edges of torn supraspinatus compared to the control subscapularis tendon [90]. Wu et al. showed that the percentage of cells undergoing apoptosis increased gradually with the degree of ECM breakdown [91]. Many biochemical events lead to apoptosis, as modification of the cellular membrane (blebbing), nuclear fragmentation, DNA fragmentation, and modification of cell adhesion [92]. Cytochrome C proteins are cellular signaling proteins which activate the synthesis of caspases, a protease enzyme family which promotes the degradation of cellular contents [93]. In an in vitro study, Lee et al. found an increased expression of cytochrome C and caspases in injured rotator cuff tendons compared to controls, confirming the increased apoptosis in turned supraspinatus tendons [94]. On the other hand, the turnover of ECM is mediated by MMPs, which are able to denature collagen fibers. The fine balance between suppression and induction of the MMPs is of primary importance for the homeostasis of the ECM. An increased activity of MMP-1 and a reduction of MMP-2 and MMP-3 have been described by many authors in a supraspinatus tendon rupture, confirming that the failure of the normal matrix remodeling process is an important element in RCTs [95]. Castagna et al. found these increased enzyme levels not only at the edges of the torn supraspinatus, but also in uninjured portions of the supraspinatus and the subscapularis tendons, which suggests that a more global breakdown of tissue may occur [96].

The variances in the genetic code between individuals are termed single nucleotide polymorphisms (SNPs), and Tashjian et al. identified 2 SNPs associated with RCTs [97]. They were located within two genes SAP30BP (on chromosome 17) and SASH1 (on chromosome 6). These genes both play a marked role in apoptosis, regulating tendon cell apoptosis and predisposing individuals to RCTs. Recently the same authors identified an SNP within the estrogen-related receptor beta (ESRRB) gene that appears to promote increased susceptibility to retears after a rotator cuff repair [98].

2.3 Rotator Cuff Healing

2.3.1 The Tendon Repair Process

The tendon healing process can be divided into three successive and overlapping phases, defined respectively as inflammatory phase (0–7 days), proliferative phase (5–25 days), and remodeling phase (>21 days) [99].

The goals of tendon repair are to restore its force transmission function and recreate the relationships with the surrounding tissues which allow the tendon to move smoothly. The success of tendon healing depends on the activation

of cellular elements able to synthesize a new ECM and to remodel it with structural properties suitable for sustaining tensile loads. Two mechanisms have been proposed to explain the recruitment of these cellular elements [99]: the first hypothesis, of "extrinsic repair," states that fibroblasts responsible for the synthesis of ECM are not resident in the tendon but migrate to the lesion from the bloodstream; the second hypothesis, of "intrinsic repair," states that these cells are resident in the endothenonium and in the epithenonium and from there directly migrate to the lesion site. It is likely that both the mechanisms coexist and are activated in two successive moments; the initial stages of the repair would be guided by nonresident cells, recalled by chemotactic factors released at the time of injury, while the remodeling phases would be promoted by resident cell populations, which migrate later to the lesion site [100].

2.3.1.1 Inflammatory Phase

In the initial inflammatory phase, damage to the vascular structures causes extravasation of blood inside the tendon and formation of hematoma. Activation of the coagulation cascade and of platelets releases chemotactic factors, vasodilatory substances, and proinflammatory molecules, which attract inflammatory cells at the site of the lesion. These cells release other cytokines such as IL-1β and tumor necrosis factor α, which further promote the inflammatory cascade [101].

This early response to rotator cuff tears leads to apoptosis of tenocytes and degradation of muscle fibers; cellular debris, clot, and foreign material are then removed by phagocytosis from granulocytes and macrophages, which secrete additional signaling molecules involved in chemotaxis and in the regulation of cell differentiation. Most of these factors are members of the transforming growth factor β superfamily and are the key regulators of gene expression, allowing subsequent tissue regeneration to occur [102]. At the end of the inflammatory phase, fibroblasts are recruited, and begin to synthesize the components of the ECM and release angiogenic factors, which activate vascular proliferation and promote the formation of a new capillary network [103].

2.3.1.2 Proliferative Phase

In the proliferative (or fibroblastic or "repair") phase, the recruitment of fibroblasts continues and their proliferation increases, as well as the synthesis of collagen and of other molecules of the ECM. Collagen production during tendon repair begins with the synthesis of type III collagen, which takes on a disordered disposition and gives the lesion a histological appearance similar to that of dermal scars [104].

In the muscle, anti-inflammatory macrophages express myogenic regulatory factors, which in combination with other endocrine growth factors can induce the development of mature myocytes from precursor cells [105, 106].

2.3.1.3 Remodeling Phase

The remodeling phase is characterized by a reduction of the synthesis of ECM and of type III collagen and an increase in the synthesis of type I collagen. Type I collagen fibers are arranged longitudinally along the axis of the tendon load and cross-links are formed that stabilize the fibers. At the end of this phase, the maximum stiffness and tensile strength of the tendon is reached, which however remains lower than that of a healthy tendon [100, 104].

2.3.2 Patients' Factors Affecting Tendon Healing

Numerous studies described factors influencing rotator cuff healing after surgical repair, including age, smoking habits, comorbidities, tear size, and fatty infiltration of the rotator cuff muscles. These factors, together with variables related to the surgical technique and the rehabilitation protocol, contribute to define the healing potential of a repaired rotator cuff.

2.3.2.1 Age

Increasing age negatively affects rotator cuff healing [107, 108]. This is both related to the reduction of the tendons' intrinsic healing prop-

erties and to the fact that age also increases the probability of having concomitant extrinsic factors, which increase the likelihood of postoperative retears. A recent retrospective cohort study on 1600 consecutive rotator cuff repairs identified age as an independent factor strongly related to increasing retear after rotator cuff repair. Interestingly, the retear risk appeared to increase at different rates as the patient age increased (minimally under 50 years of age, by 5% for each decade between the ages of 50 and 70 years and substantially over 70 years of age) [109]. An age >70 years at the time of surgery was also identified as an independent risk factor in a study designed to determine the prognostic factors that predict rotator cuff healing after surgical repair [110]. These findings are confirmed by ex vivo and animal studies, which identified a loss of the structural organization of tendons and a decrease of collagen organization and repair integrity with increasing age [111, 112].

2.3.2.2 Cigarette Smoking

Smoking affects the biomechanical and histological properties of rotator cuff tendons: this has a consequence both on the risk of developing rotator cuff tears [67] and on the healing properties after rotator cuff repair. The fact that smokers have a significantly higher healing failure rate than nonsmokers was postulated considering the results of animal studies and was recently confirmed in a prospective cohort study [113, 114]. Abstinence or at least decrease in nicotine use is recommended to improve healing after rotator cuff repair [99].

2.3.2.3 Endocrine Disorders and Hormones

Abnormal glucose levels impair the biomechanical properties of rotator cuff in animal models and increase the number of complications (infections and repair failures) after rotator cuff repairs in human patients [115, 116]. It is therefore recommended to evaluate and normalize the blood glucose levels pre- and postoperatively.

Hyperlipidemia and hypercholesterolemia decrease the biomechanical properties of rotator cuff tendons in animal models and have been considered as risk factors for the development of RCTs [41, 44, 50]. Recently, the negative role of hyperlipidemia has been documented also in a clinical study with a retrospective design [117].

Estrogens could also play a role influencing rotator cuff healing: estrogen deficiency, in fact, was associated with decreased biomechanical properties and poor development of chondroid tissue at the tendon-to-bone junction after rotator cuff repair in an animal model: this could encourage investigations on agents which modulate bone metabolism, to improve tendon-to-bone healing in patients with an estrogen deficiency who undergo rotator cuff surgery [118].

Low levels of vitamin D showed to negatively influence early healing of the rotator cuff after repair in animal models [119], but these effects could not be proved in human clinical studies [120].

2.3.3 Intraoperative Variables and Surgical Technique

The surgical technique can also affect rotator cuff healing. Numerous procedures have been described to address rotator cuff lesions, evolving from open to fully arthroscopic techniques; simultaneously, sutures and devices to secure the repaired tendon to the humeral head have been optimized, with the constant aim of providing a mechanically stable repair at the tendon-to-bone junction [121, 122]. However, not every massive RCT can be treated with the same surgical technique. The macroscopic observation of the tendon and its grade of mobilization can guide the surgeon to the best choice among the numerous options available; furthermore, predictive scores, like the ARoCuS score, have been developed to help the surgeon in this decision-making process [123].

Drilling into the footprint or performing microfractures of the greater tuberosity have been proposed as solutions to enhance tendon healing, with contrasting results among the available reports. Although not visible in postoperative magnetic resonance imaging, healing seems to be positively affected by microfractures, especially in case of larger tears [124]. Drilling into the footprint is another solution which could contribute

to rotator cuff healing [125, 126]. The rationale behind these techniques, which demonstrated to improve the quality of repair tissue and biomechanical strength at the tendon-to-bone insertion after rotator cuff repair in animal models, is the stimulation of bone marrow-derived cell infiltration into the repaired rotator cuff [127]. To perform a debridement of the torn tendons is another surgical trick which could improve postsurgical rotator cuff healing. This is commonly recommended in presence of large retracted lesions, although recent evidence suggests that detaching the intact tendon, completing and repairing the rotator cuff lesion, could enhance healing as compared to in situ repair techniques for partial lesions [128].

2.3.4 Timing of Surgery and Rehabilitation

Animal studies suggest that, when possible, early surgical repair of traumatic massive RCTs should be performed, since this leads to improved biomechanical properties of the tissue after healing [129]. This recommendation, however, still deserves to be confirmed in the clinical setting [130]. Delaying repair of massive lesions induces fatty degeneration of the involved tendons, which can also influence structural and clinical outcomes: fatty degeneration of the rotator cuff tendons is, in fact, an independent risk factor for rotator cuff retears and for worse outcome in patients with large to massive tears who had intact tendons after repair [107, 131, 132].

A high quality meta-analysis by Riboh et al. showed no statistically significant difference between immobilization and early passive motion in rotator cuff retear rates at minimum of 1 year of follow-up, but suggested the possibility of an increase in retears with early passive motion protocols [133]. Kluczynski et al. concluded their meta-analysis associating early active motion with increased risk of structural defects for small and large rotator cuff tears. The current, best available evidence regarding postoperative rehabilitation after rotator cuff repair is a recently published systematic review of overlapping meta-analyses, which suggests that early motion improves the range of motion after rotator cuff repair but increases the risk of rotator cuff retear [134].

2.3.5 Predictive Models to Quantify Tendon Healing

As this chapter synthetically illustrated, numerous patient-related factors may play a role in determining both subjective and objective outcomes of rotator cuff surgery. The rotator cuff healing index was recently developed as a numerical scoring system to predict rotator cuff healing after surgical repair. This promising system, for which validation studies are expected, includes clinical and radiological factors and has been designed to help predict the adequacy of the repair and assist in deciding the appropriate treatment options [110].

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