Pathology of Rotator Cuff Tears

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Introduction

Rotator cuff injuries are common, especially above the age of 60 and have an effect not only on shoulder function but also on the overall health status and quality of life of the patients [28]. Codman first attempted to describe rotator cuff tear pathology in 1934 [8]. Since then many theories have been proposed in order to explain the underlying pathology and efforts have been made to define the predicting factors leading to rotator cuff tears. During the last decades the factors contributing to this complicated disease have been teamed into two major categories: the extrinsic and the intrinsic factors.

Extrinsic factors actually involve anatomic and demographic variables that predispose to supraspinatus tears, while intrinsic factors include pathologic and degenerative changes into the substance of the tendon and the muscle itself.

Nowadays, it is thought that in most cases both extrinsic and intrinsic factors play a significant role in rotator cuff pathology. Despite the progress of molecular biology, many issues concerning the pathogenesis of this disease remain unknown and have not been fully understood to date.

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Extrinsic Factors

Impingement and Acromial Shape

In 1987, Neer et al. [31], after intraoperative observation of 400 patients, suggested that the impingement of the tendon to the anterior third of the acromion is responsible for 95% of tears. This hypothesis was emphasized by observations from Bigliani et al. [4] that the degree of impingement was dependent on the acromial shape. They demonstrated that the shape of the acromion varied in the sagittal plane and proposed three types for it: Type I (flat), Type II (curved), and Type III (hooked acromion). Additionally, a positive correlation was found between the type of the acromion and the presence of rotator cuff tear,

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with Type III having the worst influence on unobstructed tendon movement in the subacromial space [4, 25, 42]. In the early 1990s Neer's hypothesis gained universal acceptance and either open or arthroscopic subacromial decompression was established as a very successful means for relieving shoulder pain associated with cuff pathology.

However, subsequent studies suggested that Type II and III acromions were not congenital [35, 44]. Furthermore, progression from Type I to Type III acromion was found to be related to age [42]. Traction forces applied from the coracoacromial ligament to the anterior third of the acromion appear to lead to the formation of a spur at this area [35]. Additionally, many researchers found that subacromial decompression alone did not always guarantee pain relief for the patients [10, 17].

Nowadays, it is well documented that rotator cuff tears usually start on the articular side and not from the bursal side, which renders pure impingement of the rotator cuff leading to attritional changes rather unlikely. It is still thought that impingement on the traction related acromial spur may indirectly contribute to rotator cuff pathology, but its "mechanical" role is not believed to be as important as was thought before [19].

Demographic Factors

A number of demographic variables are also included in extrinsic factors. However, most demographic factors have been poorly investigated, and little quality data is available.

The association between hand dominance, mechanical overuse, and rotator cuff pathology is relatively well documented. Yamaguchi et al. [43] stated that tears are often more symptomatic in the dominant than in the nondominant arm. However, 36% of those with a symptomatic full-thickness tear had a co-existing asymptomatic full-thickness tear in the contralateral nondominant side. In addition, ultrasonographic investigation revealed the likelihood of this rising to 50% in patients older than 60 years old [43].

Another demographic parameter with negative influence on rotator cuff integrity is smoking. Recently, Baumgarten et al. observed in humans a strong association between smoking and rotator cuff disease. It is very important to note that supraspinatus tears appear to have a dose and a time-dependent relationship with smoking [2].

Nicotine is also strongly correlated with poorer outcomes following rotator cuff repairs. Rat animal model studies, as well as clinical investigations revealed that nicotine can have deleterious effects on tendon healing and smokers have significantly reduced postoperative function, increased pain scores and less patient satisfaction [12, 26].

Finally, other factors such as diabetes mellitus have been associated with decreased ability of tendon healing after rotator cuff repairs [6].

Intrinsic Factors

The term intrinsic factors encompasses a variety of mechanisms that occur within the rotator cuff itself. Among the theories proposed, age-related degeneration and repetitive microtrauma seem to be the most reliable models explaining the mechanism of cuff disease. However, we must take into account the role of cuff vascularity as well as the neural theory for tendinopathy.

Degeneration and Microtrauma Theory

Epidemiological studies with ultrasound examination revealed a positive correlation between age and supraspinatus tendon tear prevalence [39]. More specifically, the frequency of these tears increased from 13% in the youngest group (50–59 years) to 20% (60–69 years), 31% (70–79 years), and 52% in the oldest group (80–89 years) [39]. It is important to note though, that the majority of the examined patients were asymptomatic. This observation leads to the hypothesis that rotator cuff tear may be a "normal" aging process.

Histological studies support the previous hypothesis of an ongoing degenerative process contributing to rotator cuff disease. Loss of cellularity and vascularity, as well as fibrocartilage mass formation are age-related changes frequently found at the site of cuff insertion [1, 27]. In a recent study Hashimoto et al. [16] found seven characteristic histological findings in torn rotator cuff:

1. Thinning and disorientation of the collagen fibers
2. Myxoid degeneration
3. Hyaline degeneration
4. Vascular proliferation (34%)
5. Fatty infiltration (33%)
6. Chondroid metaplasia (21%)
7. Intratendinous calcification (19%)

We have to lay emphasis on the fact that vascular proliferation and fatty infiltration were seen only on the bursal side of the cuff. The remaining five histological changes were found on the articular side as primary degenerative "reducers" of tendon tensile capacity [16, 18].

Moreover, in an effort to detect molecular-biochemical mediators influencing rotator cuff pathology Premdas et al. [34] observed a high level of Smooth Muscle Actin (SMA) in the nonvascular connective tissue near the edges of the torn rotator cuff. SMA in vitro causes contraction of the collagen-glycosaminoglycan compounds. In vivo, this action may lead to contraction of the torn cuff edges, increasing the distance at the repair margin and inhibiting primary healing.

Great importance must be given on the role of altered collagen fiber quality [21]. Generally, the central zone of the

healthy supraspinatus tendon is primarily composed of Type I collagen fibers with smaller amounts of Type III collagen, decorin, and biglycan. On the other hand, the primary component at the zone of tendon insertion (tendon's footprint) is Type II collagen, which can withstand better compressive loads. Histological findings in the diseased rotator cuff reveal alteration in the type of collagen at the fibrocartilaginous zone from Type II to Type III, with a subsequent tendon ability to withstand compressive loads [24]. However, it is not well known whether this change is an age-related "physiological" degeneration or the result of repetitive overuse and microinjury.

Parallel to degeneration, the microtrauma theory suggests that repetitive overload stresses lead to micro-injuries and lacerations within the tendon mass that are not given sufficient time to heal before further trauma occurs. The "roots" of this theory can be found back in 1934, when Codman demonstrated that partial tears of the tendon began in the articular side, where the load capacity is lower than in the bursal side [7].

A further question is what the role of inflammatory reaction is during these repetitive overload stresses. For this reason Soslowksy et al. [37] created an animal rat model, mirroring the repetitive motion of the supraspinatus under the acromial arch. They observed downregulation of gene expression in transforming growth factor beta-1 (TGF-β1), increase in cellularity, loss of collagen orientation, and alterations in gross cell morphologic characteristics. It is important that by the end of 13 weeks the tendon had a higher cross sectional area but could withstand lower load to failure. In another rat model study using the reverse-transcriptase polymerase chain reaction (RT-PCR), acute increase in angiogenic markers (VEGF) (400% in 3 days) and subacute increase in COX-2 (300% in 8 weeks) was observed [33].

Ex vivo studies investigated the biochemical cascade of interleukin-1 beta (IL-1β) on human tendon cells. They revealed an increase of COX-2 leading to higher levels of prostaglandin E2 (PGE2) [40]. At the same time, an elevation of the levels of matrix metalloproteases (MMP), specifically MMP-1, MMP-3, and MMP-13, was found. Numerous other studies revealed an increase of the aforementioned inflammatory mediators during tensile loading of supraspinatus tendon [20, 22]. Although the significance of IL-1β in cuff tears remains unknown in vivo, it is believed that COX-2 and PGE2 are mainly pain mediators and MMPs lead to loss of tissue architecture.

Despite the fact that inflammatory mediators are present, histological studies in cadaveric and postsurgical specimens with rotator cuff tears did not show any significant chronic inflammatory reaction. Benson et al. [3] found morphological evidence of degeneration and edema within the extracellular matrix, amyloid deposition (20%), but no evidence of chronic inflammation with few B- or T-lymphocytes present in patients that underwent subacromial decompression. The only indirect finding of a chronic inflammatory process is the revascularization noted either intraoperatively [16] or with Doppler ultrasound [32].

In vivo studies of rotator cuff tear pathology did not prove a significant role in the inflammatory reaction in the degenerative process [3].

Oxidative Stress and Apoptosis

In 2002, Yuan et al. demonstrated the presence of increased concentration of apoptotic cells at the edge of the torn rotator cuff tear (34%) compared with normal tendons (13%) [45]. Further studies demonstrated that exposure of cultured human rotator cuff tendon cells to oxidative stress via administration of H_2O_2 resulted in increased concentrations of key apoptotic mediators such as cytochrome–C and caspase-3 within the cells [46]. Finally, in vivo studies in human torn rotator cuff revealed decreased levels of a novel antioxidant peroxidase, peroxiredoxin 5 (PRDX5). Induced overexpression of PRDX5 results in reduction of apoptosis by 46% [47]. All the previous studies suggest that oxidative stress has an important role in supraspinatus tendinopathy and tear.

Murrel and his team made a great effort to explore the mediators of this oxidative reaction and to propose a possible model pathway [41]. According to their findings in torn supraspinatus specimens in vivo, two key mediators were found to play an important role: Matrix metalloproteinase (MMP-1) within the extracellular matrix and c-Jun N-terminal protein kinase (JNK) within the intracellural matrix.

MMP-1 levels are elevated within damaged tendons, leading to loss of tissue architecture, decreased collagen synthesis, and abnormal tendon biomechanics. Moreover, JNK is a mitogen-induced protein kinase that is induced in tendons by IL-1 and by cyclic mechanical stretch [36] (Fig. 1). JNK, when phosphorylated, activates a number of transcription factors linked to the apoptotic pathway [9]. When JNK-specific inhibitors were used, there was a reduction in MMP levels and tendon disruption. A possible model pathway is illustrated in Fig. 2.

Rotator Cuff Vascularity

In 1990, Lohr and Uhthoff [23] reported that there is a critical hypovascular zone 10–15 mm proximal to the insertion of the supraspinatus tendon. Since then, this area and its exact role became a matter of debate. Other studies [5, 30] examining capillary distributions, vessel number, and diameter found that no significant hypovascular areas exist.

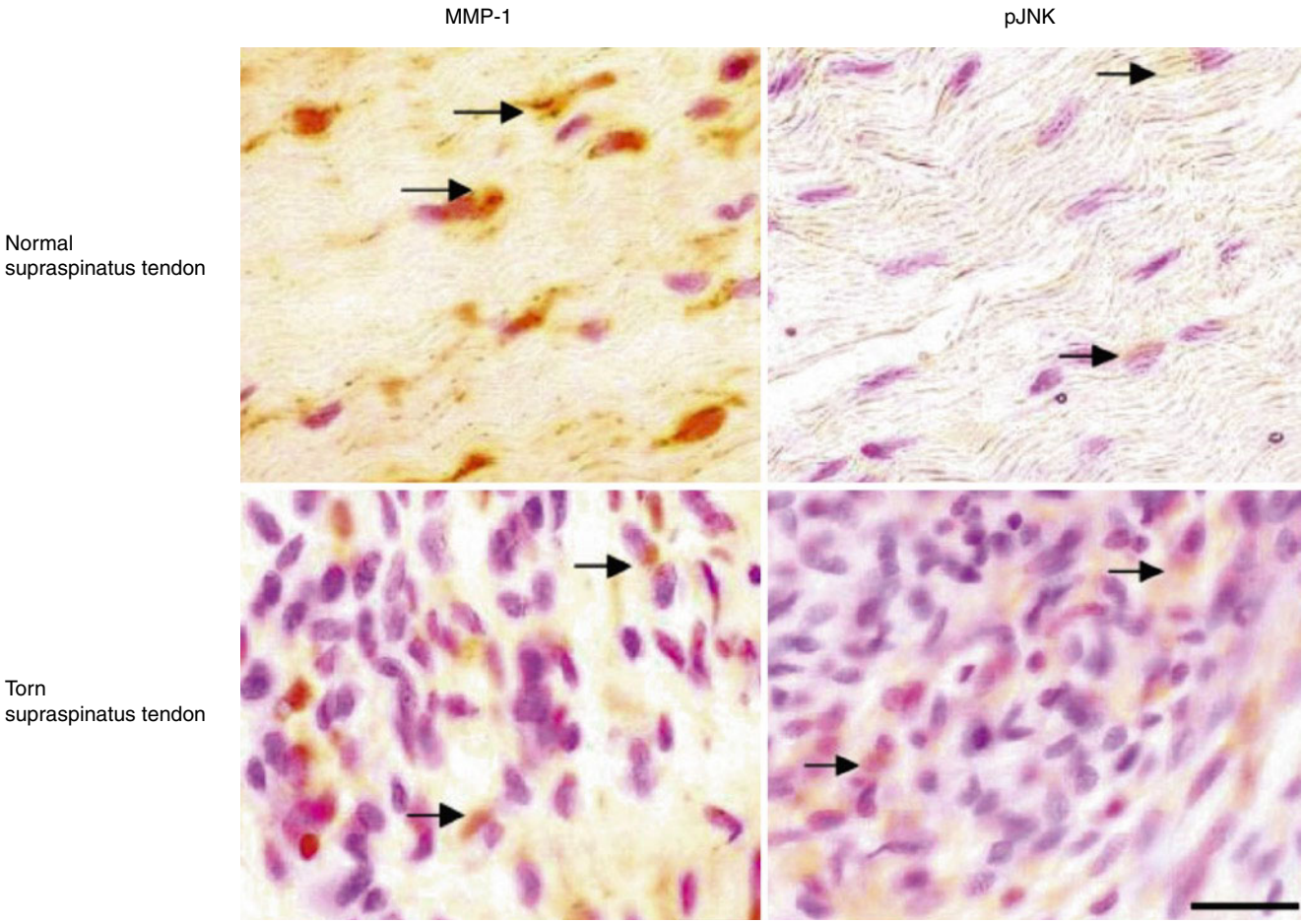

Fig. 1 Immunohistochemical detection of phosphorylated JNK and MMP1 in the longitudinal sections of rotator cuff tendons [41]

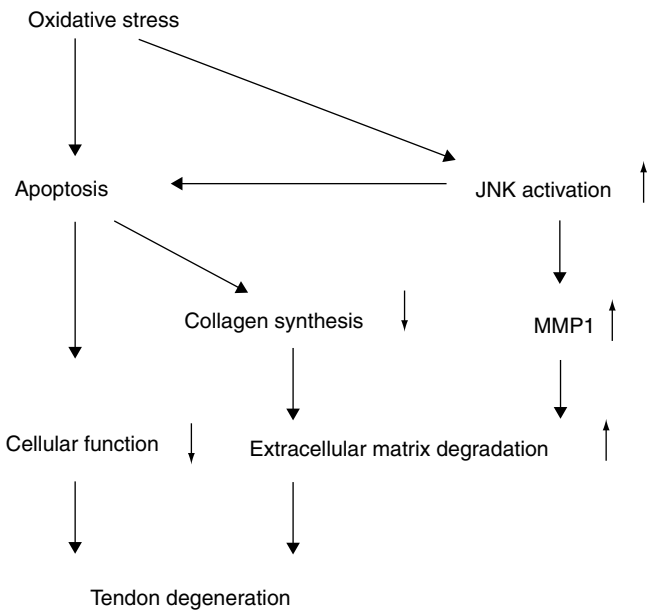

Fig. 2 Possible pathway of tendon degeneration under oxidative stress [41]

Moreover, recent histological and immunohistochemical studies in torn tendons revealed relative hyperperfusion at this "critical" area [11]. Additionally, intraoperative laser Doppler flowmetry showed again hyperperfusion at the tear edge [38] casting considerable doubt on the importance of the supraspinatus critical zone.

Questions have been raised if arterial perfusion can be reduced during full arm adduction or during compression at the humeral head.

Neural Theory of Tendinopathy

In 2006, Molloy et al. [29] observed in a rat model increased expression of a range of glutamate-signaling proteins after overuse. Culture of tendon cells in glutamate led to increase of their apoptotic frequency. It is important to note that glutamate is a peptide associated with the central nervous system and is already involved in the pathogenesis of tendon degeneration. Additionally, high concentrations of substance P have been related with the diseased rotator cuff [13]. It is

possible that the neural overstimulation observed, leads to painful symptoms, disorganization of cuff architecture, and structural weakness that subsequently results in a tear. Previous observations constitute the cornerstone of the neural theory, which remains controversial but constitutes an exciting source for future research.

Genetic Influences in Rotator Cuff Tears

Besides the presented theories, lately, questions have been raised on the importance of the underlying genetic susceptibility to the pathology of rotator cuff.

Recent studies [14, 15] have shown that genetic influences may exist. An increased incidence of supraspinatus tears in siblings of patients with known tears was recently observed. It has also been suggested that genetic factors may influence the progression and the size of the tear, as well as the presence of pain in the medium term [14, 15].

Genetic factors may play their role not only in the development but also in the progression of full thickness tears. However, further studies are needed to provide more solid data on this issue.

Summary

The overall incidence of full-thickness tears in the general population ranges between 7% and 27%, and that of partial-thickness tears between 13% and 37%. Not all of them are symptomatic. Theories on the cause of these tears range from purely mechanical or attritional damage to intrinsic age-related degeneration. Whether intrinsic or extrinsic factors contribute to the occurrence of tears and to what extent is still not clear. However, alteration of the cellular and extracellular matrix, with evidence of an apoptotic process within the tendon, has been noted in a number of studies, but the exact pathway for this is still unclear.

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