Basic Science in Rotator Cuff Tears

Abstract

Rotator cuff (RC) tears are the most common soft tissue injuries of the shoulder. Despite the surgical improvement with new techniques in the repair site of the tears, the clinical results remain with high rate of failure. Different experimental studies in many animal models try to evaluate the complexity of the clinical problem. In this review article we summarize the knowledge from studies regarding the tendon to bone repair and healing, the early inflammatory reaction, the bone, tendon and muscle condition and the diversity of scaffolds that have been used in order to bridge a gap between RC tendon and the recipient site on bone. To answer the spectrum of questions regarding the treatment of RC tears further specific knowledge using the aforementioned animal models is compulsory.

Keywords: Rotator Cuff Tear; Tendon to Bone Healing; Animal model; Mini review; Basic Science

Introduction

Rotator cuff (RC) tears are one of the most common clinical problems of upper extremity causing shoulder pain and functional loss. The impact of this condition to the socio-economic status of the society is quite significant and cannot be overlooked. In 2002 alone, approximately 40,000 surgical operations were performed in USA at the cost of $14,000 per surgery. There is an ever-growing increase in the number of surgical interventions of RC tears and RC repairs remain as one of the most common operations performed [1].

More than 18 million people report shoulder pain in USA [2]. Overall RC tear prevalence is estimated up to 19% of the population, especially in patients over 60 years old it can be as high as 50% [3-5]. The therapy for full thickness RC tears includes conservative and surgical treatment, but despite new techniques and new fixations, the results remain suboptimal [6,7]. Over the past few years a lot of basic science articles were published regarding etiology, therapy and postoperative treatment of RC tears.

Etiology

It is well known that both intrinsic and extrinsic mechanisms have been accused of causing rotator cuff tendon injury and tears. Nonetheless, primary intrinsic degeneration of the tendon better interprets RC pathology.

There are several factors that predict the risk for symptoms: tear size, symptoms, location, age, activity level, muscle quality and nerve function is among the most important of them. Animal models are being used to enhance our understanding of the role of these factors to RC pathology and to find predictors for a successful RC repair.

Tendon condition

There is plethora of animal and cadaveric studies assessing the tendon to bone fixation and healing. On different animals studies the authors show not only how the tendon behaves after a massive tear in the course of time but also how the tendon heals to bone in acute and chronic tendon RC tears. Furthermore, on cadaveric studies the strength of tendon to bone fixation and the anatomy of the area are evaluated.

There are different methods to repair full thickness RC tears with the most common being the double row (DR) technique. Recently Fei W et al. [8] showed, in their animal studies, better biomechanical and histological results with suture bridge repair (SB) as opposed to double row repair. The authors showed that the SB suture method provided better anatomical reduction of the RC footprint and better healing with more compact collagen fibers extending naturally from the tendon to cancellous bone. The difference in morphology of the bone-tendon interface may be attributed to the difference in bone-tendon contact pressure.

The RC repair site responds initially with inflammatory reaction and the first 3 days are characterized by multinucleated cells, whereas lymphocytes and plasma cells present in days 7 to 10 [9-11]. Angiogenesis starts from day 3 to 10. The repair site becomes stiffer and the ultimate force increases during the postoperative period. Collagen I, collagen III, TGFbeta-1, mRNA, cell proliferation and density significantly increase at the 10th postoperative day and achieve a plateau by 56 days.

On the other hand, the characteristics of the tendon to bone healing differ substantially from the normal tendon insertion site. The biomechanical and histological characteristics of the repair area remain inferior to the uninjured sites [9-11].
Regarding the tendon to bone gap, a number of scaffolds have been used to bridge the tendon defect. Despite the complexity of healing tissue engineering, research is focused on different approaches as biphasic [12] and triphasic scaffolds have been generated with multiple cell types, electrospun nanofibrous, polymer scaffolds with gradients in mineral content, to better mimic the tendon to bone insertion site. More recently Libner J et al. [14] presented a new mineralization protocol for creating a tendon to bone scaffold, attempting to provide more stiffness in the repair area using the mechanics of PLGA nanofiber scaffolds [14]. Thomopoulos et al. [15] attempted to protect with primary immobilization the insertion site of RC repair to allow the expression of type III collagen, decorin and biglycan (extracellular matrix) until the insertion site reformed and then to start passive exercise. Peltz et al. [16-20] with their studies demonstrated that after 2 weeks of passive motion, range of motion improved and joint stiffness decreased compared to immobilization The same authors published better results after short (2 weeks) or moderate (4 weeks) period of immobilization before starting the exercise program.

**Bone condition**

The bone condition indicates that bone loss may play a significant factor in poor healing. In order to resolve this problem there are few studies that investigate bone density and condition at the insertion site of RC. Galatz L et al. [21] examined the bone density at the greater tuberosity after acute and chronic RC tears with peripheral quantitative computed tomography. Their results indicated that bone density decreases faster in acute and slower in chronic RC tears. According to the authors bone loss may be the cause in poor tendon healing when a RC repair is delayed.

To improve bone density at the RC footprint and to stabilize its viscoelastic properties Cadet E et al. [22] worked on a rat model. The authors proved that bone density and stiffness in the footprint area were higher when the rats received bisphosphonates.

**Muscle condition**

Most of the experimental studies focus mainly in chronic RC tears because in these conditions there are mainly structural changes to the muscles. A variety of animals (mainly rats, rabbits, dogs and sheep) are used as experimental models to explore these changes [23-35]. The dysfunction of chronic RC tears’ might not recover after an RC repair and Coleman’s [36] designated this condition as ‘point of no return’ suggesting reconstructing the RC at early stages as acute tears. The different types of muscles fibers initially switch and later transform in fatty atrophy. An early repair of the RC tear led to a faster recovery of both muscle function and tendon elasticity compared to a more delayed repair.

To examine in vivo the muscle force and the histologic changes (Figures 1-3) in a 3-dimensional (3-D) manner, Ditsios et al. [36] used the established a rat shoulder model [37] to evaluate massive rotator cuff tears by sectioning supraspinatus (SS) and infraspinatus (IS) tendons. The author showed that a low functional outcome in a repair of a chronic RC tear may be attributed to the decrease in muscle power during their repair and secondly to the higher degree of degeneration in their dorsal part.

![Figure 1A & B: Transverse muscle sections were obtained at levels Z, localized every 6000 mm (Zk + 1/4 Zk + 6000 mm with k = 1/4 1.5), where the first Z1 and the last level Z5 were at a plane 1000 mm from the lateral and medial ends of the detached muscle. B Nine optical fields (3 zones: ventral, central, dorsal) were taken at displacement steps of 1200 mm in the x-axis and 1000 mm in the y-axis. Each coordinate X2Y1 (+ 1/4 1.5, + 1/4 1.5) corresponds to an optical field (873 628) mm.](image-url)

Itoigawa et al. [38] studied the molecular mechanism of fatty muscle infiltration after an RC tear by investigating the expression of genes in vitro and then testing their expression profiles in vivo in a model. The author underlined the cardinal role of expression of gene Wnt10b which is suppressed when no mechanical muscle tension exists.

Further analysis of fatty infiltration in molecular level provided results of increased expression of adipogenic genes PPARc and C/EBPα, which when in absence adipogenesis is prohibited [39]. Likewise the RC muscle atrophy is proportionally analogous to the size of RC tears [40-42].

From the pharmacological view, anabolic steroids (nandrolone) group and insulin-like growth factor (IGF) were found to decrease the catabolic face of RC tears [43].
Nerve - muscle function

Biomechanical and histological studies evaluate the structural components of RC muscles but these results do not explain how the nerves react with supraspinatus and infraspinatus muscles especially in chronic cases [44]. A great number of studies demonstrates the nerve behavior and the complex couple excitation-contraction following RC tenotomy [45,46].

Muscle dysfunction with chronic RC tears demonstrated with electromyographic studies show how the compound motor action potential (CMAP) amplitude [46] decreases compared to the contralateral control shoulder. However EMG studies provide information only for the activated part of the muscle near to the electrode [47].

In a recent study the authors developed a new technique for measuring the nerve reaction 4 months after the initial cutting of supraspinatus (SS) and infraspinatus (IS) tendons in insertions site. Their data demonstrate that the muscles extensively lost mass especially in the tendon – muscle dorsal part area and the force decreased more 30% in SS and 35% in IS respectively [36].

Conclusion

Consequently, there are many experimental studies describing the structural, histological, functional changing during time. Most of them emphasize in chronic massive rotator cuff tears and evaluate with CT, MRI, biomechanical, biochemical, electrophysiological, general and molecular histological and gene test but even with all that new knowledge there are many questions to answer in the futures.

Despite the plentiful of studies, there are many questions to address or to be elucidated regarding RC tears’ behavior during healing process. Certainly, animal models closely resemble the respective alterations observed in humans, and useful conclusions can be derived.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

Acknowledgement

Declared none.

References

1. Oh LS, Wolf BR, Hall MP, Levy BA, Marx RG (2007) Indications for rotator cuff repair: A systematic review. Clin Orthop Relat Res 455: 52-63
2. Christopher C Schmidt, Claudius D Jarrett, Brandon T Brown (2015) MME Management of Rotator Cuff Tears J Hand Surg Am 40(2): 399-408.
3. Lohr JF, Uhthoff HK (2007) Epidemiology and pathophysiology of rotator cuff tears. Orthopade 36(9): 788-795.
4. Yamanaka K, Matsumoto T (1994) The joint side tear of the rotator cuff. A followup study by arthrography. Clin Orthop Relat Res 304(1): 120-127.
5. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA (2006) The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 88(8): 1699-1704.
6. Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K (2004) The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am 86(2): 219-224.
7. Pealy S, Adler RS, Drakos MC, Kelly AM, Allen AA, et al. (2006) Patterns of vascular and anatomical response after rotator cuff repair. Am J Sports Med 34(1): 120-127.
8. Fei W, Guo W (2015) A biomechanical and histological comparison of the suture bridge and conventional double row techniques of the repair of full-thickness rotator cuff tears in a rabbit model. BMC Musculoskelet Disord 16(16): 148.

9. Galatz LM, Sandell L, Rothermich SY, Das R, Mastrny A, et al. (2006) Characteristics of the supraspinatus tendon during tendon-to-bone healing after acute injury. J Orthop Res 24(3): 541-550.

10. Galatz L, Rothermich S, VanderPloeg K, Petersen B, Sandell L, et al. (2007) Development of the supraspinatus tendon-to-bone insertion: localized expression of extracellular matrix and growth factor genes. J Orthop Res 25(12): 1621-1628.

11. Kim HM, Galatz LM, Das R, Havioglou N, Rothermich SY, Thomopoulos S (2011) The role of transforming growth factor beta isoforms in tendon-to-bone healing. Connect Tissue Res 52(2): 87-98.

12. Wang IN, Shan J, Choi R, Oh S, Kepler CK, et al. (2007) Role of osteoblast-fibroblast interactions in the formation of the ligament to bone interface. J Orthop Res 25(12): 1609-1620.

13. Spalazzzi JP, Doty SB, MoBiF KL, Levine WN, Lu HH (2006) Development of controlled matrix heterogeneity on a triphasic scaffold for orthopedic tissue engineering. Tissue Eng 12(12): 3497-3508.

14. Lipner J, Liu W, Liu Y, Boyle J, Genin GM, et al. (2014) The mechanics of PLGA nanofiber scaffolds with biomimetic gradients in mineral for tendon-to-bone repair. J Mech Behav Biomed Mater 40: 59-68.

15. Thomopoulos S, Williams GR, Soslowsky LJ (2003) Tendon to bone healing: differences in biomechanical, structural, and compositional properties due to range of activity levels. J Biomech Eng 125(1): 106-113.

16. Peltz CD, Dourte LM, Sarver JI, Kim SY, Williams GR, et al. (2008) Immobilization with Daily Passive Motion Causes Detrimental Changes in Shoulder Joint Mechanics in a Rat Model of Rotator Cuff Injury and Repair. Trans Orthop Res Soc 33: 251.

17. Peltz CD, Dourte LM, Kuntz AF, Sarver JI, Kim SY, et al. (2008) The effect of postoperative passive motion on rotator cuff healing in a rat model. J Bone Joint Surg Am 91(10): 2421-2429.

18. Peltz CD, Dourte LM, Sarver JI, Kim SY, Williams GR, et al. (2009) Exercise Following Immobilization Is Detrimental to Tendon Properties and Joint Mechanics in a Rat Rotator Cuff Injury Model. Trans Orthop Res Soc 34: 1504.

19. Peltz CD, Dourte LM, Kuntz AF, Sarver JI, Williams GR, et al. (2009) Range of Motion Loss Is Transient Following Six Weeks of Immobilization in a Rat Model of Rotator Cuff Repair. Trans Orthop Res Soc 34: 1895.

20. Peltz CD, Dourte LM, Kuntz AF, Sarver JI, Williams GR, et al. (2009) Following a Moderate Period of Immobilization, Tendon Properties and Joint Mechanics Are Not Altered With Exercise. Trans Orthop Res Soc 34: 1896.

21. Galatz LM, Rothermich SY, Zaegeel M, Silva MJ, Havioglou N, et al. (2005) Delayed repair of tendon to bone injuries leads to decreased biomechanical properties and bone loss. J Orthop Res 23(6): 1441-1447.

22. Cadet ER, Voors GC, Rahman R, Park SH, Gardner TR, et al. (2010) Improving bone density at the rotator cuff footprint increases supraspinatus tendon failure stress in a rat model. J Orthop Res 28(3): 308-314.

23. Gimbel JA, Mehta S, Van Kleunen JP, Williams GR, Soslowsky LJ (2004) The tension required at repair to reappose the supraspinatus tendon to bone rapidly increases after injury. Clin Orthop Relat Res 426(426):258-265.

24. Gimbel JA, Van Kleunen JP, Lake SP, Williams GR, Soslowsky LJ (2007) The role of repair tension on tendon to bone healing in an animal model of chronic rotator cuff tears. J Biomech 40(3): 561-568.

25. Matsumoto F, Ulthoff HK, Trudel L, Loehr JF (2002) Delayed tendon reattachment does not reverse atrophy and fat accumulation of the supraspinatus—an experimental study in rabbits. J Orthop Res 20(2): 357-363.

26. Bowshen K, Hadley S, Pham K, Caiazza V, Lee TQ, et al. (2010) Development of fatty atrophy after neurologic and rotator cuff injuries in an animal model of rotator cuff pathology. J Bone Joint Surg Am 92(13): 2270-2278.

27. Rubino LJ, Sprott DC, Stille HF Jr, Crosby LA (2008) Fatty infiltration does not progress after rotator cuff repair in a rabbit model. Arthroscopy 24(8): 936-940.

28. Ulthoff HK, Matsumoto F, Trudel G, Himori K (2003) Early reattachment does not reverse atrophy and fat accumulation of the supraspinatus—an experimental study in rabbits. J Orthop Res 21(3): 386-392.

29. Derwin KA, Bakar AR, Gods MJ, Iannotti JP (2007) Assessment of the canine model of rotator cuff injury and repair. J Shoulder Elbow Surg 16(5 Suppl): S140-S148.

30. Coleman SH, Fealy S, Ehteshami JR, MacGillivray JD, Alteck DW, et al. (2003) Chronic rotator cuff injury and repair model in sheep. J Bone Joint Surg Am 85(12): 2391-2402.

31. Gerber C, Meyer DC, Schneeberger AG, Hoppeler H, von Re- chenberg B (2004) Effect of tendon release and delayed repair on the structure of the muscles of the rotator cuff: an experimental study in sheep. J Bone Joint Surg Am 86(9): 1973-1982.

32. Peters KS, Lam PH, Murrell GA (2010) Repair of partial thickness rotator cuff tears: a biomechanical analysis of footprint contact pressure and strength in an ovine model. Arthroscopy 26(7): 877-884.

33. Santoni BG, McGilvray KC, Lyons AS, Bansal M, Turner AS, et al. (2010) Biomechanical analysis of an ovine rotator cuff repair via porous patch augmentation in a chronic rupture model. Am J Sports Med 38(4): 679-686.

34. Ugen C, Dines J, McGarry M, Grande D, Lee T, Limpsivasti O (2010) The effect of recombinant human platelet derived growth factor BC-coated sutures on rotator cuff healing in a sheep model. Arthroscopy 26(11): 1456-1462.

35. Coleman SH, Fealy S, Ehteshami JR, MacGillivray JD, Alteck DW, et al. (2003) Chronic rotator cuff injury and repair model in sheep. J Bone Joint Surg Am 85(12): 2391-2402.

36. Ditsios K, Boutsiadis A, Kapoukranidou D, Chatzisotiriou A, Kalpidis L, et al. (2014) Chronic massive rotator cuff tear in rats: in vivo evaluation of muscle force and three-dimensional histologic analysis. J Shoulder Elbow Surg 23(12): 1822-1830.

37. Soslowsky LJ, Carpenter JE, DeBano CM, Banerji I, Moalli MR (1996) Development and use of an animal model for investigations on rotator cuff disease. J Shoulder Elbow Surg 5(5): 383-392.
38. Itoigawa Y, Kishimoto KN, Sano H, Kaneko K, Itoi E (2011) Molecular mechanism of fatty degeneration in rotator cuff muscle with tendon rupture. J Orthop Res 29(6):861-866.

39. Gerber C, Fuchs B, Hodler J (2000) The results of repair of massive tears of the rotator cuff. J Bone Joint Surg Am 82(4):505-515.

40. Melis B, DeFranco MJ, Chuinard C, Walch G (2010) Natural history of fatty infiltration and atrophy of the supraspinatus muscle in rotator cuff tears. Clin Orthop Relat Res 468(6): 1498-1505.

41. Schmutz S, Fuchs T, Regenfelder F, Steinmann P, Zumstein M, et al. (2009) Expression ofatrophy mRNA relates to tendon tear size in supraspinatus muscle. Clin Orthop Relat Res 467(2): 457-464.

42. Wieser K1, Farshad M, Meyer DC, Konze P, von Rechenberg B, et al. (2015) Tendon response to pharmaco-mechanical stimulation of the chronically retracted rotator cuff in sheep. Knee Surg Sports Traumatol Arthrosc 23(2): 577-584.

43. Mannava S, Callahan MF, Trach SM, Wiggins WF, Smith BP, Koman LA, Smith TL, Tuohy CJ (2011) Chemical denervation with botulinum neurotoxin a improves the surgical manipulation of the muscle-tendon unit: an experimental study in an animal model. J Hand Surg Am 36(2): 222-231.

44. Gajdosik RL (2001) Passive extensibility of skeletal muscle: review of the literature with clinical implications. Clin Biomech 16(2): 87-101.

45. Jamali AA, Afshar P, Abrams RA, Lieber RL (2000) Skeletal muscle response to tenotomy. Muscle Nerve 23: 851-862.

46. Mannava S, Plate JF, Whitlock PW, Callahan MF, Seyler TM, Koman LA, Smith TL, Tuohy CJ (2011) Evaluation of in vivo rotator cuff muscle function after acute and chronic detachment of the supraspinatus tendon: an experimental study in an animal model. J Bone Joint Surg Am 93(18): 1702-1711.

47. Lieber R (2010) Skeletal muscle structure, function, and plasticity: the physiological basis of rehabilitation. Wolters Kluwer Health/Lippincott Williams & Wilkins, Baltimore, USA.