Biological aspects of rotator cuff healing

Britt Wildemann
Franka Klatte

Julius Wolff Institute, Center for Musculoskeletal Surgery
Berlin-Brandenburg Center for Regenerative Therapies
Charité - Universitätsmedizin Berlin, German

Corresponding author:
Britt Wildemann
Julius Wolff Institute, Center for Musculoskeletal Surgery
Berlin-Brandenburg Center for Regenerative Therapies
Charité - Universitätsmedizin Berlin
Augustenburger Platz 1, 13353 Berlin, German
e-mail: britt.wildemann@charite.de

Summary

Tendon tears of the rotator cuff show a high prevalence in today's population. Patients suffer from permanent pain and disability, and surgical reconstruction may be the only possibility for abatement. The complex process of tendon-bone healing leads to mechanically inferior scar-tissue, which often results in retears or non-healing. In the current literature, factors such as patients age, sex and fatty muscle infiltration are highly correlated to the presence of rotator cuff tears and the incidence of retears. To improve the tendon tissue quality after surgical reconstructions biologically based strategies with use of growth factors arouse more and more interest in the last years. However, to optimize the treatment of rotator cuff tears the biological background of tears and retears must be investigated in more detail. This article will elucidate different aspects that have an impact on rotator cuff healing and give a brief insight in tendon/ligament cell culture and animal studies focusing on growth factor treatments.

Key words: age, fatty infiltration, growth factors, rotator cuff rupture, sex, tenocytes

Introduction

The shoulder joint is composed of three bones and the rotator cuff as a group of four muscles and their tendons, allowing movement and providing stability. In general, tears of the rotator cuff cause symptoms, such as persistent pain, disability, decreased range of motion and strength and very often a surgical reconstruction is needed. Rotator cuff tears are dependent on different clinical, demographic or radiological determined risk factors. A possible biological or cellular background of this correlation is not jet clarified. The main complication of rotator cuff tears is the high retear rate. Therefore the biological augmentation of the tendon-bone healing with growth factors was highly debated in the last years. Different growth factors were analyzed for a positive influence on tendon/ligament cell cultures or in animal studies. However, no treatment option with growth factor could be transferred to clinical practice so far.

Clinical problem: Rotator cuff tears and retears

Rotator cuff tears can be caused by injury resulting in an acute tear or by degeneration as a result of for example increasing age, repeated overload or impingement. Partial tears are often asymptomatic, but can develop to complete tears. Tears of the rotator cuff are a relevant clinical problem and reason for millions of physician visits annually in the US (1). A surgical reconstruction is very often indicated, but does not lead to complete regeneration of a normal tendon-bone insertion site, but rather to formation of a weaker scar tissue (2). Within the last years the surgical techniques were improved (3-6). The main complication for rotator cuff repair, however, represents non-healing or retear of the tendon insertion site depending on factors such as patients age, sex and grade of fatty muscle infiltration (1, 7-13). Despite these observed risk factors, surgical rotator cuff repair is carried out identically between different patient clusters with no respect to potential biological differences. A further limitation is the fact that the currently discussed risk factors are based upon clinical and radiographic studies of observative nature and cannot provide causal answers on the biologic differences between different patient subgroups.

Risk factors influencing tendon integrity and healing

The incidence and the outcome after rotator cuff reconstructions depend on different biological and clinical factors. As an important biological factor, the age of the patient is highly correlated to the incidence of tendon tears and retears (1, 8, 11, 13). A study analyzing individuals with an asymptomatic shoulder found that partial or full-thickness tears strongly increase after the age of 50, and 80% of individuals older than 80 years had an unrecognized rotator cuff tear (11). The incidence of retears increased after the age of 60 (8) and Boileau reported on only 43% of patients in which tendons completely healed after the age of 65 (7). Some authors observed an influence of sex (14, 15), while others did not (1, 11, 16). For the biological factor sex sexual hormones, such as estrogen, were hypothesized to influence the healing. It was found that estrogen affected the collagen synthesis after acute exercise in tendon connective tissue (17). Gender as a "social" factor, including differences such as personality traits, attitudes, behaviors,

and cultural background, might also influence the healing outcome. A 2011 published study found higher levels of pre- and post-operative disability in women with rotator cuff pathology. They concluded that the biological aspect sex and the "social" aspect gender, defined in this study as expectations, participation limitation, and satisfaction, are important for the seen differences (18). The effect of another "social" factor in terms of working activity on shoulder disorders was investigated by van Rijn et al. (19). The literature review revealed no association between the job and rotator cuff tears or suprascapular nerve compression, but a correlation between repetitive work, awkward postures and forceful exertion in work with subacromial impingement syndrome. It is discussed controversially in the literature if the subacromial impingement syndrome is a cause of rotator cuff tears or if it is the effect of rotator cuff diseases. The different theories of the impingement syndrome were discussed in detail by Campbell and Dunn (20). Nicotine consumption (21), obesity and diabetes (14, 22) negatively influence the healing after rotator cuff surgery. A correlation of Statin-medication, which is a cholesterol lowering drug, and tendon tears was also hypothesized (23). It was discussed that a chronic, low-grade inflammation, as seen in patients with obesity and diabetes, represents a prolonged disruptive factor of tendon healing. Reason for this may be a reduced number of circulating macrophages in the acute inflammation phase, which may result in a less effective early healing (22). Furthermore several radiological determined factors influence the healing outcome. The radiographic grade of fatty muscle infiltration (according to Goutallier) (24) is strongly correlated to the rate of retears and the clinical outcome after rotator cuff reconstructions (8-10, 12). Thereby a Goutallier grade of 1 was shown to be the cutoff between tendon integrity and recurrent tears (10). In addition, the initial tear size (according to Boileau) (7) and the tendon retraction (according to Patte) (25) are correlated with the clinical outcome (26-28). To get more information about the influence of several factors on the healing outcome, Chung et al. included 272 patients in a study and found a significantly increased failure rate depending on the lower bone mineral density (BMD), older age, female sex, larger tear size, higher fatty muscle infiltration, diabetes, and shorter acromiohumeral distance (14). After multivariate analysis, however, only the BMD and the fatty muscle infiltration were an independent determining factor. Also the rehabilitation program after rotator cuff surgery influences the healing outcome. For example, a supervised physical therapy seems to be superior compared to home exercise (29) and nurse invented T-bar device led to improved range of motion in patients with shoulder surgeries (30). Furthermore, the correlation of genetic factors and the incidence of tendon diseases were hypothesized (31), but specific "tendon pathology" genes could not be identified so far, since it is a multifactorial disease. The main challenge is to understand the gene interactions and signaling pathways involved in tendon diseases (32). These partially heterogeneous findings from the clinical evaluation of rotator cuff healing in relation to different clinical, biological and "social" aspects, as summarized in Figure 1, highlight the importance of more detailed investigations. In-depth epidemiological data on the influence of these conditions are missing, likely due to the fact that the patients cannot easily be grouped in only one category. It is unclear, which of these biological or clinical factors play the key role in rotator cuff regeneration. To answer this question, further studies also on the molecular and cellular background of rotator cuff tears and retears are urgently needed.

Biology of tendon healing

The healing of tendon tears is briefly summarized in the following: after injury of the tendon the repair process starts to restore normal function by reestablishing the tendon fibers. In the first phase, the inflammation occurs immediately after injury by the disruption of blood vessels and the formation of a hematoma. Cytokines are released and different cell types such as erythrocytes, platelets, neutrophils, monocytes and macrophages migrate to site of injury. The invading cells remove cell debris and secret further cytokines and extracellular matrix proteins. The released angiogenic factors in-

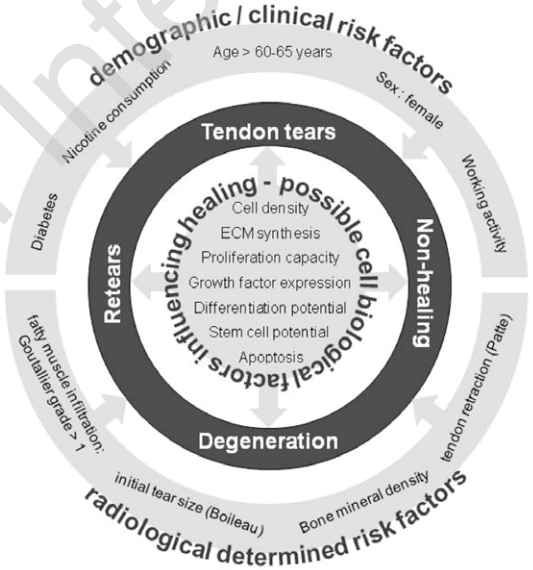

Figure 1. Demographic, clinical, radiological determined and possible cell biological risk factors influencing tendon healing outcome.

duce the formation of new vessels. Following this phase the proliferation of cells occur with further extracellular matrix production. During this proliferative phase an unorganized, highly cellularized and vascularized tissue forms that builds the initial scar tissue. At a later time point the remodeling phase starts. If the mechanical boundary conditions are given and the biology is not disturbed, the number of cells and vessels within this scar tissue decreases. The ratio between Collagen type I (Col-I) and Collagen type III (Col-III) fibers changes toward more Col-I and the fibers arrange longitudinally along the tendon axis, providing the mechanical strength of the tendon (33, 34). As a matter of course, numerous growth factors play an important role in the complex process of tendon healing, which is reviewed in detail by Oliva et al. (34). However, as mentioned earlier, the tendon

tissue shows only a repair and no regeneration, meaning a fully reconstruction of the original tissue does not occur.
Little is known about the biology of retears, degeneration and non-healing of the rotator cuff. From a molecular perspective it was reported that torn or degenerated tendons show a higher amount of Col-III and a decreased amount of Col-I (35). Furthermore, degenerated tendons express higher amounts of cartilage markers such as Collagen type II (Col-II), aggrecan and sox9 and lower amounts of tendon related genes (36). Another study revealed that autophagic cell death, apoptosis and myofibroblast cell differentiation rise and cell density fall with tendon extracellular matrix (ECM) degeneration (37). In rat Achilles tendon, more rounded tenocyte nuclei and reduced number of tenocytes were found with increasing age (38). With increasing tear-size reparative and inflammatory processes, as well as the cellular activity of the tenocytes decreased, while chondroid redifferentiation and amyloid deposition increased (28). Furthermore a modified tissue structure (27) and more than 20% higher rates of apoptosis (39) were reported.

Growth factors for tendon/ligament healing

To improve the tendon tissue quality and biological response following surgical reconstructions, biologically based strategies have gained increasing interest over the past years. The most important cellular components in the tendon are tenocytes, but also tendon-derived stem cells or tendon progenitor cells were identified previously (40, 41). In general, the regenerative capacity of the tenocytes or tendon-derived stem cells (e.g. cell activity, proliferation, ECM synthesis) should be targeted. Tenocytes exhibit very low proliferative capacity and may benefit from biological support by growth factors. Therefore, it was suggested that the use of growth factors could improve tendon healing (42). But which growth factor should be chosen?
Positive *in vitro* and *in vivo* effects of growth factors such as Bone Morphogenetic Protein (BMP)-12 (43-46) or BMP-13 (47, 48), Transforming Growth Factor β (TGF-β) (49-52), Insulin-like Growth Factor I (IGF-I) (53), Platelet-derived Growth Factor (PDGF) (53-58), Growth and Differentiation Factor 5 (GDF-5) (59-61), Vascular Endothelial Growth Factor (VEGF) (54, 62, 63), and basic Fibroblast Growth Factor (bFGF) (49, 53-55, 64, 65) were shown. One of the main parameter analyzed in the *in vitro* experiments was the stimulation of cell proliferation and the expression or production of collagens of tendon fibroblasts. Additionally, *in vivo* an improved healing with increased biomechanical strength was found. So far no single growth factor treatment for rotator cuff repair could be transferred to clinical use. However, autologous platelet-rich plasma (PRP) was, as a pilot study, clinically applied to patients who underwent arthroscopic rotator cuff repair surgeries by Randelli et al. (66, 67). The first study showed a reduced pain score and increased functional score compared to a pre-operative time point (66). The second study revealed a pain reduction for the PRP treated patients in the early postoperative time (until 30 days) compared to the non-PRP treated patient group, but no differences in functional scores and healing rates 6, 12, and 24 months after surgery were found (67). Further studies on the clinical PRP application in different fields of orthopedic surgery are reviewed by Foster et al. The critically evaluation shows also limitations of the studies, which often lack control groups or are limited in case series (68). Therefore, further clinical studies are necessary. A summary of studies regarding growth factor treatment of tendon cell cultures or tendon/ligament healing is shown in Table 1 and 2. However, this summary makes no claim to be complete. The mentioned studies focus not exclusively on cells isolated from tendons of the rotator cuff or rotator cuff repair, but include also studies on Anterior Cruciate Ligament (ACL), Patellar, Achilles or Flexor Tendon reconstructions.
The main complications for rotator cuff repair are retears at the tendon-bone insertion site. For tendon-bone healing of the rotator cuff it could therefore be useful to treat osteoblasts and tenocytes simultaneously. Therefore, the members of the TGF-β superfamily, BMP-2 and BMP-7, which are already clinically used for the treatment of bone defects, could be promising. Additionally to their positive effect on bone healing they seem to improve tendon healing, as it was reported in several *in vivo* studies: BMP-2 led to improved tendon-bone healing with increased biomechanical strength after anterior cruciate ligament (ACL) reconstructions (69, 70), flexor tendon reconstructions (71), or transplantation of the long digital extensor tendon to a bone tunnel (72). Similar positive effects were described for BMP-7 used in experimental ACL repair (73). In addition, several *in vitro* studies revealed effects of BMP-2 and BMP-7 on tendon cell cultures. Contrary results were observed for BMP-2 treatment on tenocytes. In a previous study, we found positive effects on Col-I expression and synthesis in tenocyte-like cells and a decrease in cell activity with use of BMP-2 in higher concentrations (1000ng/ml) (74). Other groups found no effects of BMP-2 (49, 54). BMP-7 application to ligament or tendon cell cultures resulted in a stimulated cell proliferation/activity and Col-I synthesis (74-77).
Studies on the effect of BMP-2 or BMP-7 on tenocytes of patient clusters differing in terms of age, sex or fatty muscle infiltration are not available.

Table 1. *In vitro* growth factor studies.

GF	Cell origin	Dosage	Effect	Ref.
BMP-2	Equine Superficial Digital FT	AdV transfection	Increased mineralization, AP expression, and Col-I synthesis	(45)
	Human SSP Tendon	100, 500, 1000ng/mL	Increased Col-I synthesis; decreased cell activity	(74)
	Murine Achilles Tendon cell lines	500ng/mL	Increased AP activity, AP and Osterix expression	(49)
	Canine FT	20, 50, 100ng/mL	No change of cell proliferation and Collagen production	(54)
BMP-7	Human SSP Tendon	100, 500,1000, 2000ng/mL	Increased cell activity, Col-I expression and synthesis	(74)
	Rat MCL	50, 100, 200, 300, 400ng/mL	Increased cell proliferation, AP activity, expression of Runx2/Cbfa1, Aggrecan, BMPR-IA, BMPR-II; decreased BMP-1, -2, -6 expression	(75)
	Bovine Digital Extensor Tendon	50, 100, 200ng/mL	Increased cell proliferation, DNA content, proteoglycan and Collagen synthesis	(76)
	Rat Achilles and Patellar Tendon	20, 50, 100, 200, 300, 400, 500ng/mL	Increased cell proliferation, Col-I, BMP-1, -3, GDF-1, -6, -8, -9, ActR-I, BMPR-IA expression; decreased SCX, Tendin, BMP-4, -6, -7 expression	(77)
BMP-12	Human Patellar Tendon	1, 10ng/mL	Increased cell proliferation, pro-Collagen-I, –III expression; decreased Decorin expression	(43)
	Chicken Tendon	AdV transfection	Increased Col-I synthesis	(44)
	Equine Superficial Digital FT	AdV transfection	Increased Col-I synthesis, COMP expression	(45)
BMP -13	human Patellar Tendon	1, 5, 10, 25, 50ng/mL	Increased cell proliferation, pro-Collagen type I; no change of Biglycan, Decorin, pro-Collagen type III expression	(47)
bFGF	Murine Achilles Tendon cell lines	5ng/mL	Increased cell proliferation	(49)
	Canine FT	10ng/mL	Increased cell proliferation, and Collagen production	(54)
	Rabbit Digitorum Profundus FT	0.5, 1, 5ng/mL	Increased cell proliferation	(53)
	Human RC Tendon	0.1, 1, 10, 100ng/mL	Increased cell proliferation, suppressed secretion of Collagens	(64)
	Canine FT	HBDS	Increased cell proliferation; Lubricin, HAS2, Decorin, MMP-1, -13 expression, decreased Col-I, -III expression	(55)
	Rat Intrasynovial tenocytes	AdV transfection	Increased Col-I, –III expression	(65)
IGF -I	Rabbit FT	10, 50, 100ng/mL	Increased cell proliferation	(53)
PDGF	Canine FT	10ng/mL	Increased cell proliferation, Collagen production	(54)
	Rabbit Digitorum Profundus FT	1, 10, 50ng/mL	Increased cell proliferation	(53)
	Canine FT	HBDS	Increased cell proliferation; decreased Col-I, -III expression	(55)
	Rat FT	Exogenous gene transfer	Increased Col-I expression	(58)
TGF-β	Murine Achilles Tendon cell lines	4ng/mL	Increased cell proliferation	(49)
	Rabbit FT	1, 5ng/mL TGF-β1, -2, -3	Increased Col-I, –III production	(50)
	Rabbit Tendon Sheath	Antisense gene transfer	Decreased Col-I, –III, TGF-β1 expression	(51)
VEGF	Canine FT	20, 50, 100ng/mL	No change of cell proliferation and Collagen production	(54)

Table 2. *In vivo* growth factor studies.

GF	Animal model	Doses	Effect	Ref.
BMP-2	Rabbit Digitorum Communis FT	15µg	Higher ultimate failure loads	(71)
	Rabbit ACL	AdV transfection	Increased stiffness and ultimate load to failure	(70)
	Canine LDET transplantation to bone tunnel	90, 180, 350, 680µg	Increased extensive bone formation, higher tendon pull-out strength	(72)
	Rabbit ISP Tendon	progenitor cell BMP-2 hydrogel	Increased fibrocartilage and bone layer, higher pull-out load	(78)
	Rabbit ACL	11.5, 50, 115µg	Increased new bone formation and stiffness, smaller tunnel diameter	(69)
BMP-7	Canine SSP model with titanium implant	3.5mg	Increased calcification, no differences in weight-bearing; stiffness, ultimate strength	(79)
	Ovine ACL	25µg	Increased new bone formation; greater strain resistance to force	(73)
BMP-12	Chicken Profundus FT	AdV transfection	Increased tensile strength and stiffness	(44)
	Ovine ISP Tendon	0.25mL of 0.35 mg/mL per hyaluronan paste	Increased maximum load and stiffness, accelerated healing	(46)
BMP -13	Rat SSP Tendon	AdV transfection	No change in new cartilage formation and Collagen fiber organization, stiffness, peak stress at failure or biomechanical strength	(48)
BMP -14	Rat Achilles Tendon	AdV transfection	Greater number of neotenocytes, greater tensile strength; no ectopic bone or cartilage formation	(80)
GDF-5	Rat Achilles Tendon	24, 55, 556ng/ cm suture	Higher ultimate tensile load and stiffness, Improved healing (histologic grading)	(59)
	Rabbit FT	55ng/cm suture	Better Soslowski histological Collagen score, better maximum load; no change in stiffness	(60)
	Rat Achilles Tendon	AdV transfection	Thicker tendons, greater cartilage formation; trend to higher strength	(61)
GF mix	Ovine ISP Tendon	1mg osteoind. bone extract	Increased new bone and fibrocartilage formation, improved load to failure	(81)
PDGF	Canine FT	100ng	Increased cell density, cell proliferation, Col-I expression, total DNA, reducible Collagen crosslinks	(56)
	Ovine ISP Tendon	75, 150, 500µg on collagen matrix	Increased load to failure and tendon to bone integration	(57)
TGF -β3	Rat SSP Tendon	HBDS, 50ng/matrix	Increased inflammation, cellularity, vascularity, cell proliferation, ultimate load, stiffness, toughness, ultimate stress, modulus	(52)
VEG F	Rat Achilles Tendon	5µg	Increased tensile strength, TGF-β expression	(62)
	Ovine ACL	tendon soaked in 5µg/mL solution	More newly formed vessels and infiltrative fibroblasts; reduced stiffness	(63)

AdV: Adenoviral
AP: Alkaline Phosphatase
COMP: Cartilage oligomeric matrix protein
FT: Flexor Tendon
GF: Growth factor
HBDS: Heparin-based delivery system
ISP: Infraspinatus
LDET: Long Digital Extensor Tendon
MCL: Medial Collateral Ligament
RC: Rotator Cuff
SCX: Scleraxis
SSP: Supraspinatus

Conclusion

Taken all together, the pathophysiology of tissue degeneration and retears of rotator cuff tendons is not yet clarified. It is obvious that tenocytes play an important role in rotator cuff tendon healing. For an optimal biologically based strategy it is of great importance to analyze the potential of the cells from different patient groups and their behavior following biological stimulation. A precisely addressed growth factor treatment together with an improved surgical technique could lead to improved osteofibroblastic integration of the tendon to the bony footprint. Potentially, certain patient clusters (for instance sex-dependent with higher age) might be associated with decreased biological activity, leading to insufficient regeneration, and might benefit from augmentation with growth factors.

References

1. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 2006; 88(8):1699-1704.
2. Rodeo SA. Biologic augmentation of rotator cuff tendon repair. J Shoulder Elbow Surg 2007; 16(5 Suppl):S191-197.
3. Pauly S, Fiebig D, Kieser B, Albrecht B, Schill A, Scheibel M. Biomechanical comparison of four double-row speed-bridging rotator cuff repair techniques with or without medial or lateral row enhancement. Knee Surg Sports Traumatol Arthrosc. 2011; 19(12):2090-2097.
4. Pauly S, Kieser B, Schill A, Gerhardt C, Scheibel M. Biomechanical comparison of 4 double-row suture-bridging rotator cuff repair techniques using different medial-row configurations. Arthroscopy 2010; 26(10):1281-1288.
5. Murray TF, Lajtai G, Mileski RM, Snyder SJ. Arthroscopic repair of medium to large full-thickness rotator cuff tears: outcome at 2- to 6-year follow-up. J Shoulder Elbow Surg 2002; 11(1):19-24.
6. Baysal D, Balyk R, Otto D, Luciak-Corea C, Beaupre L. Functional outcome and health-related quality of life after surgical repair of full-thickness rotator cuff tear using a mini-open technique. Am J Sports Med 2005; 33(9):1346-1355.
7. Boileau P, Brassart N, Watkinson DJ, Carles M, Hatzidakis AM, Krishnan SG. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? J Bone Joint Surg Am 2005; 87(6):1229-1240.
8. Cho NS, Lee BG, Rhee YG. Arthroscopic Rotator Cuff Repair Using a Suture Bridge Technique: Is the Repair Integrity Actually Maintained? The American journal of sports medicine 2011.
9. Gladstone JN, Bishop JY, Lo IKY, Flatow EL. Fatty infiltration and atrophy of the rotator cuff do not improve after rotator cuff repair and correlate with poor functional outcome. Am J Sports Med 2007; 35(5):719-728.
10. Goutallier D, Postel J, Gleyze P, Leguilloux P, van Driessche S. Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears. J Shoulder Elbow Surg 2003; 12(6):550-554.
11. Milgrom C, Schaffler M, Gilbert S, van Holsbeeck M. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. J Bone Joint Surg Br 1995; 77(2):296-298.
12. Shen P, Lien S, Shen H, Lee C, Wu S, Lin L. Long-term functional outcomes after repair of rotator cuff tears correlated with atrophy of the supraspinatus muscles on magnetic resonance images. J Shoulder Elbow Surg 2008; 17(1 Suppl):1S-7S.
13. Sørensen AKB, Bak K, Krarup AL, Thune CH, Nygaard M, Jørgensen U et al. Acute rotator cuff tear: do we miss the early diagnosis? A prospective study showing a high incidence of rotator cuff tears after shoulder trauma. J Shoulder Elbow Surg 2008; 16(2):174-180.
14. Chung SW, Oh JH, Gong HS, Kim JY, Kim SH. Factors Affecting Rotator Cuff Healing After Arthroscopic Repair: Osteoporosis as One of the Independent Risk Factors. The American journal of sports medicine 2011.
15. Grasso A, Milano G, Salvatore M, Falcone G, Deriu L, Fabbriciani C. Single-row versus double-row arthroscopic rotator cuff repair: a prospective randomized clinical study. Arthroscopy 2009; 25(1):4-12.
16. Tashjian RZ, Hollins AM, Kim H, Teefey SA, Middleton WD, Steger-May K et al. Factors affecting healing rates after arthroscopic double-row rotator cuff repair. Am J Sports Med 2010; 38(12):2435-2442.
17. Magnusson SP, Hansen M, Langberg H, Miller B, Haraldsson B, Westh EK et al. The adaptability of tendon to loading differs in men and women. Int J Exp Pathol 2007; 88(4):237-240.
18. Razmjou H, Davis AM, Jaglal SB, Holtby R, Richards RR. Disability and satisfaction after rotator cuff decompression or repair: a sex and gender analysis. BMC Musculoskelet Disord 2011; 12:66.
19. van Rijn RM, Huisstede BM, Koes BW, Burdorf A. Associations between work-related factors and specific disorders of the shoulder - a systematic review of the literature. Scand J Work Environ Health 2010; 36(3):189-201.
20. Campbell RSD, Dunn A. External impingement of the shoulder. Semin Musculoskelet Radiol 2008; 12(2):107-126.
21. Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S. Nicotine delays tendon-to-bone healing in a rat shoulder model. J Bone Joint Surg Am 2006; 88(9):2027-2034.
22. Battery L, Maffulli N. Inflammation in overuse tendon injuries. Sports Med Arthrosc 2011; 19(3):213-217.
23. Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990-2005 and review of the literature. Arthritis Rheum. 2008; 59(3):367-372.
24. Goutallier D, Postel JM, Bernageau J, Lavau L, Voisin MC. Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin. Orthop. Relat. Res. 1994; (304):78-83.
25. Patte D. Classification of rotator cuff lesions. Clin. Orthop. Relat. Res. 1990; (254):81-86.
26. DeFranco MJ, Bershadsky B, Ciccone J, Yum J, Iannotti

JP. Functional outcome of arthroscopic rotator cuff repairs: a correlation of anatomic and clinical results. J Shoulder Elbow Surg 2007; 16(6):759-765.
27. Matthews TJW, Hand GC, Rees JL, Athanasou NA, Carr AJ. Pathology of the torn rotator cuff tendon. Reduction in potential for repair as tear size increases. J Bone Joint Surg Br 2006; 88(4):489-495.
28. Matthews TJW, Smith SR, Peach CA, Rees JL, Urban JPG, Carr AJ. In vivo measurement of tissue metabolism in tendons of the rotator cuff: implications for surgical management. J Bone Joint Surg Br 2007; 89(5):633-638.
29. Holmgren T, Oberg B, Sjöberg I, Johansson K. Supervised strengthening exercises versus home-based movement exercises after arthroscopic acromioplasty: A randomized clinical trial. J Rehabil Med 2011.
30. Wang C, Lin P, Lee Y, Chuang C, Tsay S, Chu C. Using a nurse invented T-Bar device in a rehabilitation program improved the range of motion for rotator cuff repair patients. Journal of clinical nursing 2012; 21(1-2):121-128.
31. Gwilym SE, Watkins B, Cooper CD, Harvie P, Auplish S, Pollard TCB et al. Genetic influences in the progression of tears of the rotator cuff. J Bone Joint Surg Br 2009; 91(7):915-917.
32. Longo UG, Berton A, Papapietro N, Maffulli N, Denaro V. Epidemiology, genetics and biological factors of rotator cuff tears. Med Sport Sci 2012; 57:1-9.
33. James R, Kesturu G, Balian G, Chhabra AB. Tendon: biology, biomechanics, repair, growth factors, and evolving treatment options. J Hand Surg Am 2008; 33(1):102-112.
34. Oliva F, Via AG, Maffulli N. Role of growth factors in rotator cuff healing. Sports Med Arthrosc 2011; 19(3):218-226.
35. Maffulli N, Ewen SW, Waterston SW, Reaper J, Barrass V. Tenocytes from ruptured and tendinopathic achilles tendons produce greater quantities of type III collagen than tenocytes from normal achilles tendons. An in vitro model of human tendon healing. Am J Sports Med 2000; 28(4):499-505.
36. Archambault JM, Jelinsky SA, Lake SP, Hill AA, Glaser DL, Soslowsky LJ. Rat supraspinatus tendon expresses cartilage markers with overuse. J. Orthop. Res. 2007; 25(5):617-624.
37. Wu B, Chen J, Rosa TD, Yu Q, Wang A, Xu J et al. Cellular response and extracellular matrix breakdown in rotator cuff tendon rupture. Arch Orthop Trauma Surg 2011; 131(3):405-411.
38. Oktem H, Calgüner E, Erdoğan D, Elmas C, Gözil R, Kadioğlu D et al. [Age-related changes in light microscopy with Sirius red technique in rat Achilles tendon]. Eklem Hastalik Cerrahisi 2010; 21(1):50-55.
39. Yuan J, Murrell GAC, Wei A, Wang M. Apoptosis in rotator cuff tendonopathy. J. Orthop. Res. 2002; 20(6):1372-1379.
40. Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W et al. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat. Med. 2007; 13(10):1219-1227.
41. Rui Y, Lui PPY, Li G, Fu SC, Lee YW, Chan KM. Isolation and characterization of multipotent rat tendon-derived stem cells. Tissue Eng Part A 2010; 16(5):1549-1558.
42. Maffulli N, Moller HD, Evans CH. Tendon healing: can it be optimised? Br J Sports Med 2002; 36(5):315-316.
43. Fu SC, Wong YP, Chan BP, Pau HM, Cheuk YC, Lee KM et al. The roles of bone morphogenetic protein (BMP) 12 in stimulating the proliferation and matrix production of human patellar tendon fibroblasts. Life Sci. 2003; 72(26):2965-2974.
44. Lou J, Tu Y, Burns M, Silva MJ, Manske P. BMP-12 gene transfer augmentation of lacerated tendon repair. J. Orthop. Res. 2001; 19(6):1199-1202.
45. Murray SJ, Santangelo KS, Bertone AL. Evaluation of early cellular influences of bone morphogenetic proteins 12 and 2 on equine superficial digital flexor tenocytes and bone marrow-derived mesenchymal stem cells in vitro. Am. J. Vet. Res. 2010; 71(1):103-114.
46. Seeherman HJ, Archambault JM, Rodeo SA, Turner AS, Zekas L, D'Augusta D et al. rhBMP-12 accelerates healing of rotator cuff repairs in a sheep model. J Bone Joint Surg Am 2008; 90(10):2206-2219.
47. Wong YP, Fu SC, Cheuk YC, Lee KM, Wong MWN, Chan KM. Bone morphogenetic protein 13 stimulates cell proliferation and production of collagen in human patellar tendon fibroblasts. Acta Orthop 2005; 76(3):421-427.
48. Gulotta LV, Kovacevic D, Packer JD, Ehteshami JR, Rodeo SA. Adenoviral-mediated gene transfer of human bone morphogenetic protein-13 does not improve rotator cuff healing in a rat model. Am J Sports Med 2011; 39(1):180-187.
49. Salingcarnboriboon R, Yoshitake H, Tsuji K, Obinata M, Amagasa T, Nifuji A et al. Establishment of tendon-derived cell lines exhibiting pluripotent mesenchymal stem cell-like property. Exp. Cell Res. 2003; 287(2):289-300.
50. Klein MB, Yalamanchi N, Pham H, Longaker MT, Chang J. Flexor tendon healing in vitro: effects of TGF-beta on tendon cell collagen production. J Hand Surg Am 2002; 27(4):615-620.
51. Xia C, Ding C, Yang X, Sun K, Tian S. Effects of antisense transforming growth factor-beta1 gene transfer on the biological activities of tendon sheath fibroblasts. Orthopedics 2010; 33(8).
52. Manning CN, Kim HM, Sakiyama-Elbert S, Galatz LM, Havlioglu N, Thomopoulos S. Sustained delivery of transforming growth factor beta three enhances tendon-to-bone healing in a rat model. J. Orthop. Res. 2011; 29(7):1099-1105.
53. Costa MA, Wu C, Pham BV, Chong AKS, Pham HM, Chang J. Tissue engineering of flexor tendons: optimization of tenocyte proliferation using growth factor supplementation. Tissue Eng. 2006; 12(7):1937-1943.
54. Thomopoulos S, Harwood FL, Silva MJ, Amiel D, Gelberman RH. Effect of several growth factors on canine flexor tendon fibroblast proliferation and collagen synthesis in vitro. J Hand Surg Am 2005; 30(3):441-447.
55. Thomopoulos S, Das R, Sakiyama-Elbert S, Silva MJ, Charlton N, Gelberman RH. bFGF and PDGF-BB for tendon repair: controlled release and biologic activity by tendon fibroblasts in vitro. Ann Biomed Eng 2010; 38(2):225-234.
56. Thomopoulos S, Zaegel M, Das R, Harwood FL, Silva MJ, Amiel D et al. PDGF-BB released in tendon repair using a novel delivery system promotes cell proliferation and collagen remodeling. J. Orthop. Res. 2007; 25(10):1358-1368.

57. Hee CK, Dines JS, Dines DM, Roden CM, Wisner-Lynch LA, Turner AS et al. Augmentation of a rotator cuff suture repair using rhPDGF-BB and a type I bovine collagen matrix in an ovine model. Am J Sports Med 2011; 39(8):1630-1639.
58. Wang XT, Liu PY, Tang JB. Tendon healing in vitro: genetic modification of tenocytes with exogenous PDGF gene and promotion of collagen gene expression. J Hand Surg Am 2004; 29(5):884-890.
59. Dines JS, Weber L, Razzano P, Prajapati R, Timmer M, Bowman S et al. The effect of growth differentiation factor-5-coated sutures on tendon repair in a rat model. J Shoulder Elbow Surg 2007; 16(5 Suppl):S215-21.
60. Henn RF, Kuo CE, Kessler MW, Razzano P, Grande DP, Wolfe SW. Augmentation of zone II flexor tendon repair using growth differentiation factor 5 in a rabbit model. J Hand Surg Am 2010; 35(11):1825-1832.
61. Rickert M, Wang H, Wieloch P, Lorenz H, Steck E, Sabo D et al. Adenovirus-mediated gene transfer of growth and differentiation factor-5 into tenocytes and the healing rat Achilles tendon. Connect. Tissue Res. 2005; 46(4-5):175-183.
62. Zhang F, Liu H, Stile F, Lei M, Pang Y, Oswald TM et al. Effect of vascular endothelial growth factor on rat Achilles tendon healing. Plast. Reconstr. Surg. 2003; 112(6):1613-1619.
63. Yoshikawa T, Tohyama H, Katsura T, Kondo E, Kotani Y, Matsumoto H et al. Effects of local administration of vascular endothelial growth factor on mechanical characteristics of the semitendinosus tendon graft after anterior cruciate ligament reconstruction in sheep. Am J Sports Med 2006; 34(12):1918-1925.
64. Takahasih S, Nakajima M, Kobayashi M, Wakabayashi I, Miyakoshi N, Minagawa H et al. Effect of recombinant basic fibroblast growth factor (bFGF) on fibroblast-like cells from human rotator cuff tendon. Tohoku J. Exp. Med. 2002; 198(4):207-214.
65. Wang XT, Liu PY, Xin K, Tang JB. Tendon healing in vitro: bFGF gene transfer to tenocytes by adeno-associated viral vectors promotes expression of collagen genes. J Hand Surg Am 2005; 30(6):1255-1261.
66. Randelli PS, Arrigoni P, Cabitza P, Volpi P, Maffulli N. Autologous platelet rich plasma for arthroscopic rotator cuff repair. A pilot study. Disabil Rehabil 2008; 30(20-22):1584-1589.
67. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg 2011; 20(4):518-528.
68. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med 2009; 37(11):2259-2272.
69. Ma CB, Kawamura S, Deng X, Ying L, Schneidkraut J, Hays P et al. Bone morphogenetic proteins-signaling plays a role in tendon-to-bone healing: a study of rhBMP-2 and noggin. Am J Sports Med 2007; 35(4):597-604.
70. Martinek V, Latterman C, Usas A, Abramowitch S, Woo SL, Fu FH et al. Enhancement of tendon-bone integration of anterior cruciate ligament grafts with bone morphogenetic protein-2 gene transfer: a histological and biomechanical study. J Bone Joint Surg Am 2002; 84-A(7):1123-1131.
71. Hashimoto Y, Yoshida G, Toyoda H, Takaoka K. Generation of tendon-to-bone interface „enthesis“ with use of recombinant BMP-2 in a rabbit model. J. Orthop. Res. 2007; 25(11):1415-1424.
72. Rodeo SA, Suzuki K, Deng XH, Wozney J, Warren RF. Use of recombinant human bone morphogenetic protein-2 to enhance tendon healing in a bone tunnel. Am J Sports Med 1999; 27(4):476-488.
73. Mihelic R, Pecina M, Jelic M, Zoricic S, Kusec V, Simic P et al. Bone morphogenetic protein-7 (osteogenic protein-1) promotes tendon graft integration in anterior cruciate ligament reconstruction in sheep. Am J Sports Med 2004; 32(7):1619-1625.
74. Pauly S, Klatte F, Strobel C, Schmidmaier G, Greiner S, Scheibel M et al. BMP-2 and BMP-7 affect human rotator cuff tendon cells in vitro. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons 2011; Epub ahead of print.
75. Tsai AD, Yeh LC, Lee JC. Effects of osteogenic protein-1 (OP-1, BMP-7) on gene expression in cultured medial collateral ligament cells. J. Cell. Biochem. 2003; 90(4):777-791.
76. Yamada M, Akeda K, Asanuma K, Thonar EJA, An HS, Uchida A et al. Effect of osteogenic protein-1 on the matrix metabolism of bovine tendon cells. J. Orthop. Res. 2008; 26(1):42-48.
77. Yeh LC, Tsai AD, Lee JC. Bone morphogenetic protein-7 regulates differentially the mRNA expression of bone morphogenetic proteins and their receptors in rat achilles and patellar tendon cell cultures. J. Cell. Biochem. 2008; 104(6):2107-2122.
78. Chen C, Chang C, Wang K, Su C, Liu H, Yu C et al. Enhancement of rotator cuff tendon-bone healing with injectable periosteum progenitor cells-BMP-2 hydrogel in vivo. Knee Surg Sports Traumatol Arthrosc 2011; 19(9):1597-1607.
79. Higuera CA, Inoue N, Lim JS, Zhang R, Dimaano N, Frassica FJ et al. Tendon reattachment to a metallic implant using an allogenic bone plate augmented with rhOP-1 vs. autogenous cancellous bone and marrow in a canine model. J. Orthop. Res. 2005; 23(5):1091-1099.
80. Bolt P, Clerk AN, Luu HH, Kang Q, Kummer JL, Deng Z et al. BMP-14 gene therapy increases tendon tensile strength in a rat model of Achilles tendon injury. J Bone Joint Surg Am 2007; 89(6):1315-1320.
81. Rodeo SA, Potter HG, Kawamura S, Turner AS, Kim HJ, Atkinson BL. Biologic augmentation of rotator cuff tendon-healing with use of a mixture of osteoinductive growth factors. J Bone Joint Surg Am 2007; 89(11):2485-2497.