Knee Surg Sports Traumatol Arthrosc (2013) 21:1610–1619
DOI 10.1007/s00167-012-2145-9

SHOULDER

The science of rotator cuff tears: translating animal models to clinical recommendations using simulation analysis

Sandeep Mannava · Johannes F. Plate · Christopher J. Tuohy · Thorsten M. Seyler · Patrick W. Whitlock · Walton W. Curl · Thomas L. Smith · Katherine R. Saul

Received: 8 March 2012 / Accepted: 16 July 2012 / Published online: 29 July 2012

Abstract
Purpose The purpose of this article is to review basic science studies using various animal models for rotator cuff research and to describe structural, biomechanical, and functional changes to muscle following rotator cuff tears. The use of computational simulations to translate the findings from animal models to human scale is further detailed.
Methods A comprehensive review was performed of the basic science literature describing the use of animal models and simulation analysis to examine muscle function following rotator cuff injury and repair in the ageing population.
Results The findings from various studies of rotator cuff pathology emphasize the importance of preventing permanent muscular changes with detrimental results. In vivo muscle function, electromyography, and passive muscle–tendon unit properties were studied before and after supraspinatus tenotomy in a rodent rotator cuff injury model (acute vs chronic). Then, a series of simulation experiments were conducted using a validated computational human musculoskeletal shoulder model to assess both passive and active tension of rotator cuff repairs based on surgical positioning.
Conclusion Outcomes of rotator cuff repair may be improved by earlier surgical intervention, with lower surgical repair tensions and fewer electromyographic neuromuscular changes. An integrated approach of animal experiments, computer simulation analyses, and clinical studies may allow us to gain a fundamental understanding of the underlying pathology and interpret the results for clinical translation.

Keywords Rotator cuff · Tear · Repair · Animal model · Computational model · Botulinum neurotoxin · Ageing · Review

The authors Sandeep Mannava and Johannes F. Plate contributed equally to this work.

S. Mannava · J. F. Plate (✉) · C. J. Tuohy · T. M. Seyler · P. W. Whitlock · W. W. Curl · T. L. Smith
Department of Orthopaedic Surgery, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1070, USA
e-mail: jplate@wakehealth.edu

S. Mannava · J. F. Plate
The Neuroscience Program, Medical Center Boulevard, Wake Forest University Graduate School of Arts and Sciences, Winston-Salem, NC 27157-1070, USA

K. R. Saul
Department of Biomedical Engineering, Wake Forest School of Medicine, Winston-Salem, NC, USA

K. R. Saul
Virginia Tech-Wake Forest University School of Biomedical Engineering and Sciences, Medical Center Boulevard, Winston-Salem, NC 27157, USA

Rotator cuff tears: a clinical problem

Rotator cuff tears are a common cause of upper extremity pain and disability that results in nearly 4.5 million physician visits [51] and more than 75,000 operative repairs annually [65] in the United States. As the average age of the population increases and older patients live a more active lifestyle, the number of rotator cuff tears and repair surgeries is predicted to rise [50, 51]. Despite the surgical advances in the repair of rotator cuff tears, clinical outcomes remain suboptimal with reported re-tear rates between 20 and 70 % [16, 20]. Current treatment

recommendations for rotator cuff pathology often delay surgical intervention until conservative management options are exhausted [6, 51]. However, delayed surgical repair may result in disease progression and changes to the muscle–tendon unit [1, 15, 28, 29, 37, 48, 55], which may be irreversible [6, 46, 54, 64] and lead to suboptimal results following tear repair [24]. To gain a more fundamental understanding of rotator cuff pathology that drives clinical outcomes, it is critical to examine the complementary research being performed clinically, in animal models, and using computational approaches.

Chronic rotator cuff tears lead to structural changes of the muscle

Experiments in several animal models of rotator cuff tears have demonstrated changes to the structure and function of muscle following chronic tears, including fibre-type switching, atrophy, fatty infiltration, and reduced muscle activation. Various animal models have been employed—including rat [26, 27], rabbit [46, 53, 54, 64], dog [11], sheep [6, 23, 52, 56, 63], and non-human primates [60]—to assess the influence of tear chronicity on muscle structure and function. Previous experiments have established the rat shoulder as a suitable model for the study of human rotator cuff pathology based on the similarities in anatomic structures (Fig. 1) [61, 62]. Following chronic rotator cuff injury, the rat supraspinatus undergoes disuse atrophy, with muscle fibre-type switching to fast-muscle fibres, decreased muscle mass, and increased inter-fascicular fibrosis [1, 43]. However, the rat supraspinatus muscle does not undergo the anticipated fibrofatty infiltration of the muscle belly following tenotomy that has been observed clinically [18, 30, 38]. Studies using rabbits were able to recapitulate the fibrofatty infiltration of the supraspinatus muscle seen clinically following chronic tenotomy and suggested that the fatty infiltration seen after rotator cuff tears may result from a nerve-injury component [32, 53] or a more complex neuromuscular connectivity dysfunction [36].

Molecular analysis of fatty infiltration following chronic rotator cuff tears in a sheep model revealed increased expression of myogenic and adipogenic transcription factors [17]. The upregulation of adipogenic transcription factors *PPARγ* and *C/EBPα* was found to be the result of a reduction in *Wnt10b* expression which normally inhibits adipogenesis [35]. The extent of muscle atrophy and fibrofatty infiltration corresponds to the size of the tear and the time from injury [22, 47, 58]. The fatty infiltration changes observed in animals have been found to correspond to the size of the rotator cuff tear and time from injury in human patients clinically. Moderate fatty infiltration was found to appear at a mean of 4 years after the onset of symptoms in 1688 patients with a mean age of 57.2 years [47]. Five years after the onset of symptoms, muscle atrophy was severe [47]. While muscle atrophy following a chronic rotator cuff tear may be irreversible as shown in animal and clinical studies, progressive fibrofatty infiltration may be stopped by a timely repair [47]. Patients who presented with a re-tear following rotator cuff repair revealed rotator cuff atrophy progression, while atrophy and fibrofatty infiltration in patients with a healed repair did not progress [47].

Muscle atrophy-related genes (forkhead box protein O1, calpains, cathepsin B, ubiquitin-conjugating enzymes E2 B and E3 A) were found to be upregulated in tissue samples from human patients with rotator cuff tears [58]. Recently, the application of anabolic steroids in a rabbit rotator cuff tear model was found to decrease fibrofatty infiltration and supraspinatus tendon retraction [25], which may be a novel pharmacological approach to preserve muscle function in anticipation of surgical repair.

Electromyographic (EMG) changes in compound motor action potential (CMAP) amplitude in chronically injured rat rotator cuffs have been reported, directly relating electrophysiological rotator cuff dysfunction to time from tendon injury [43]. CMAP and area under the curve were recorded by EMG from the supraspinatus muscle, following direct suprascapular nerve stimulation. After the rat rotator cuff was chronically injured, there was lower maximal CMAP amplitude when compared to both the uninjured control and acutely injured groups.

Skeletal muscle changes following rotator cuff tears have also been described in larger animal model systems, such as sheep [6, 23] and dog [55], and revealed atrophic changes with fibrofatty infiltration [6, 23, 55]. The findings from these animal studies were confirmed in a recent clinical case series that demonstrated EMG dysfunction after rotator cuff tears, which were reversible upon rotator cuff repair [7, 41]. These studies concluded that 'reducing' the atrophied and retracted rotator cuffs during repair surgery resulted in decreased tension placed upon the suprascapular nerve as it coursed through the suprascapular or spino glenoid notch [7, 41].

In vivo biomechanics of rotator cuff repair surgery

The muscle–tendon unit structural changes described previously [1, 6, 23, 36, 53, 55] result in a stiff and retracted rotator cuff that is difficult to manipulate during surgery. In the rat model of rotator cuff tears, the tension required to re-appose the supraspinatus tendon to the humeral head has been observed to rise rapidly and progressively from the time of injury [26]. Furthermore, higher repair tensions

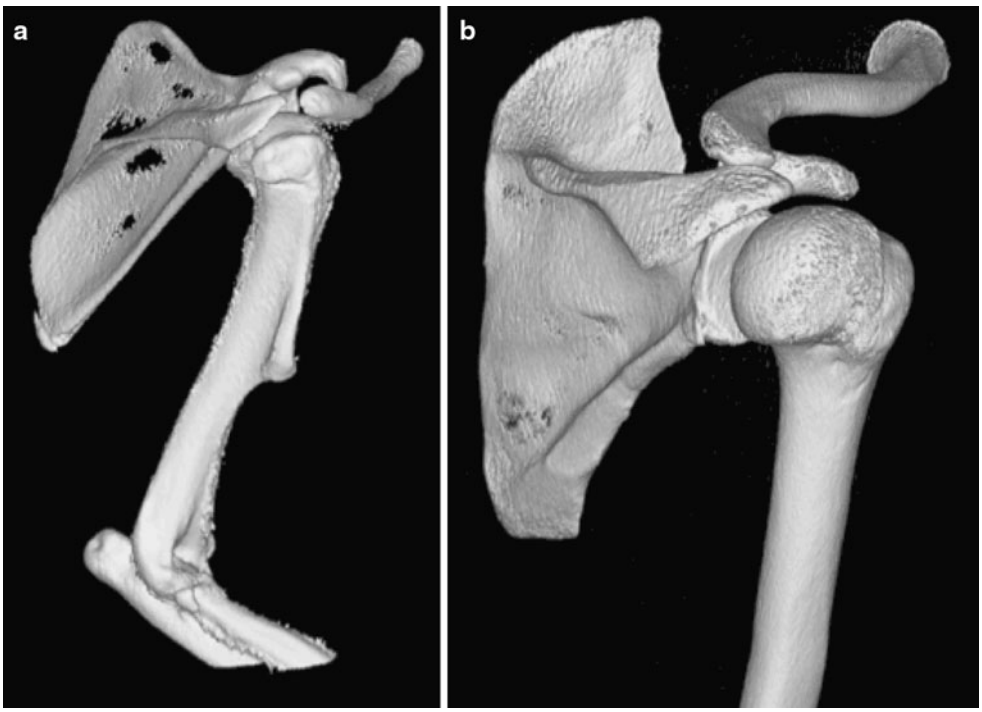

Fig. 1 Anatomic similarities between the rat and human shoulder. Three-dimensional reconstructions of computed tomography radiographic studies for rat shoulder (**a**) and for human shoulder (**b**) are depicted. The supraspinatus tendon in both species pass beneath an enclosed arch, as described by Soslowsky et al. [62] (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

were associated with a reduced quality of tendon-to-bone healing, demonstrated biomechanically with decreased load-to-failure measurements [27]. Studies in canine and sheep reported similar findings, with an increase in passive stiffness of the rotator cuff in the setting of chronically torn supraspinatus tendons [6, 23, 55]. Clinically, high repair tensions during rotator cuff repair in a study of 67 patients were correlated with inferior subjective and objective surgical outcomes [8].

Experimental evaluation of muscle function after rotator cuff tears

Studies of rotator cuff tears in animal models and cadaver studies have mainly assessed anatomic tendon-to-bone fixation during operative repair [2–4, 19, 45, 52] while in vivo functional assessments of the rotator cuff muscles in animal models or human studies following tear or repair have been limited [5, 6, 8, 13, 14, 24, 43, 49]. The structural changes in the muscle–tendon unit that result in increased repair tensions of chronic rotator cuffs have also been the subject of many investigations [6, 23, 26, 55].

Several studies have examined exercise capacity in the rabbit shoulder model, relating reduced muscle force with histological and radiographic changes that occur with disuse atrophy following rotator cuff tendon tears [5, 13, 14]. Chronic tendon tears in the sheep model were associated with atrophy, retraction, and fatty infiltration, which resulted in reduced amplitude of muscle contractile force in this chronically injured experimental group [49]. The authors concluded that computed tomography of the rotator cuff and the associated radiographic changes could only indirectly and approximately predict the reduced function [49]. Coleman et al. demonstrated that muscle function was likely to improve in the sheep model when repair was conducted in the acute tear setting. The authors suggested that when repair is undertaken in the chronic tear setting, the muscle might not recover full function. Essentially, as conservative management is pursued and surgery is delayed, their data suggest that a 'point of no return' exists where full function will not be achieved with current single-stage rotator cuff repair [6].

A recent report examined the functional consequences of rotator cuff tears in a rat model. There were three experimental groups: (1) uninjured controls; (2) acute injury (muscular function was tested 4 weeks after supraspinatus tenotomy); and (3) chronic injury (muscular function was tested 12 weeks after supraspinatus tenotomy). Histological changes in the muscle architecture were identified that were consistent with increased in vivo stiffness of the muscle–tendon unit in the acute and chronic

tear setting [43]. Then, in vivo muscle-function testing of the supraspinatus muscle–tendon unit was performed for a wide range of repair tensions, creating a comprehensive contractile amplitude versus preload/repair tension profile of rotator cuff function after injury. The data demonstrated that regardless of the experimental group, muscle function is exquisitely sensitive to preload tension [43]. Specifically, there was a 50 % reduction in maximal contractile amplitude [43] at preload tensions equivalent to the chronic repair tension required to re-appose the stiff, retracted supraspinatus muscle–tendon unit to the humeral head in this rat model [26, 27]. The findings indicate that there is a broad range of repair tensions in which the supraspinatus muscle is able to generate maximal force; however, current single-stage repair techniques, which occasionally require excessive repair tensions, reduce functional capacity significantly. Histological changes of the rotator cuff muscle and increased stiffness of the muscle–tendon unit lead to reduced muscle contractile amplitude. The study suggests that improved functional outcomes would be achieved by earlier surgical interventions for acute rotator cuff tears [31, 43], thereby avoiding what some investigators consider irreversible structural and biomechanical changes to the muscle–tendon unit.

A relationship between changes in muscle structure following tear and muscle function has also been described clinically. In a clinical study conducted by Gerber et al., thirteen patients were evaluated by magnetic resonance imaging, and fibrofatty infiltration of their rotator cuff muscles was assessed using Goutallier staging [24]. Intraoperative muscle contractile amplitude was assessed after electrical nerve stimulation and was correlated with the anatomic cross-sectional area and the amount of fibrofatty infiltration. The authors concluded that higher Goutallier staging resulted in impaired muscle function [24]. Davidson and Rivenburgh demonstrated reduced isokinetic strength in their patients when the rotator cuff was repaired under excessive tension (i.e. repair tension exceeding 8 lbs or 3.6 kg of force) [8].

Computational evaluation of muscle function after rotator cuff tears

To aid in the interpretation of the experimental evaluations of muscle function in animal studies and in the clinical settings, simulation analysis can be conducted to characterize the dependence of passive force and active moment-generating capacity on shoulder posture and tear size in the supraspinatus following surgical repair of uninjured, acute, and chronic retracted gap tendon lengths [57]. Computational musculoskeletal models are libraries of data derived from anatomic (i.e. muscle architecture, anatomic paths) and functional experiments (i.e. joint moments, muscle force) compiled into an accessible and predictive mathematical framework (Fig. 2). Computational models allow parameters to be altered to represent clinical conditions or interventions and understand the consequences in a way that would be impractical or impossible to explore in vivo (Table 1). The force that a muscle–tendon unit generates in these model systems is dependent on several factors, such as the architecture of the muscle–tendon unit (fibre length, muscle cross-sectional area, pennation, tendon length) and the stretch in the muscle and tendon, using length-dependent elements and velocity-dependent elements to capture the force-generating behaviour of muscle (Fig. 3) [68].

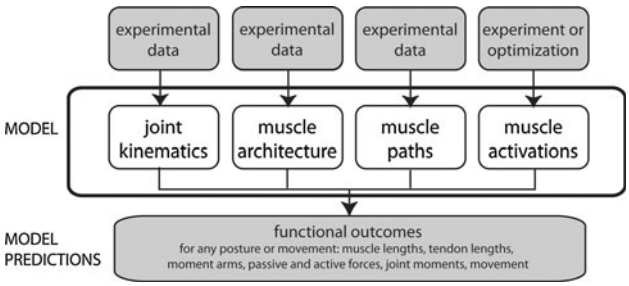

Fig. 2 Schematic diagram depicting the elements required to create an orthopaedic movement biomechanics model (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

A previously developed musculoskeletal model of the upper limb representing the anthropometry and muscle parameters of a 50th percentile male (Fig. 3) was used to simulate the consequences of a rotator cuff repair following different magnitudes of retraction [34]. Scapular and clavicular movements representing a normal shoulder rhythm are incorporated into the model [9]. The muscles crossing the shoulder are represented by 18 muscle–tendon actuators.

To represent a surgically repaired supraspinatus muscle–tendon unit, the tendon slack length was shortened by a gap distance, while the anatomic path of the muscle was maintained. Tendon slack length was shortened by 1.5 cm to represent the acute tear setting and 3 cm to represent the chronic tear setting. Passive forces were compared to previously reported values for suture pullout strength and anchoring techniques typically used in these repairs (191–287 N) [10, 39]. The calculated outcome measures included passive muscle–tendon force throughout the range of motion and active moment-generating capacity throughout abduction (Fig. 4).

Larger gap distances (simulating a chronically torn rotator cuff tendon) and smaller thoraco-humeral angles were associated with increased passive forces (Fig. 4) [57]. In certain postures, the passive tension of chronically torn supraspinatus muscle–tendon units exceeded the strength

Table 1 Applications for musculoskeletal modelling

Model parameters	Clinical conditions	Interventions
Joint kinematics	Arthritis, bony deformities	Joint replacement, arthrodesis, osteotomy
Muscle architecture	Atrophy, muscle contracture	Strength training, tendon repair, tendon lengthening
Muscle paths	Scarring	Tendon transfer
Muscle activations	Spinal cord injury, altered neural control	Functional electrical stimulation, botulinum neurotoxin A injection

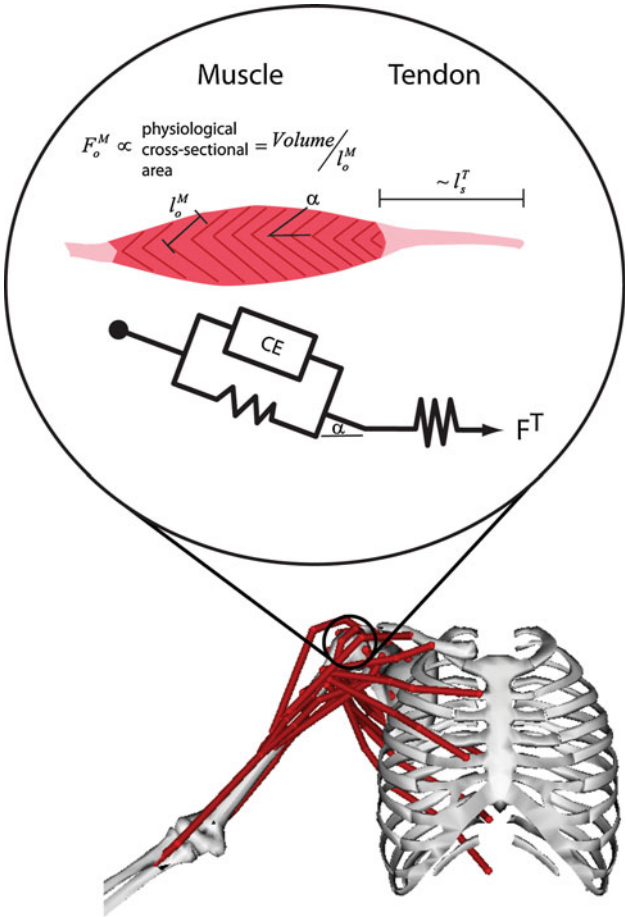

Fig. 3 The shoulder portion of the musculoskeletal model. A musculoskeletal model was developed for the upper limb representing the anthropometry and muscle parameters of a 50th percentile male [34]. Some of the parameters used for the development of this model are shown in schematic form (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

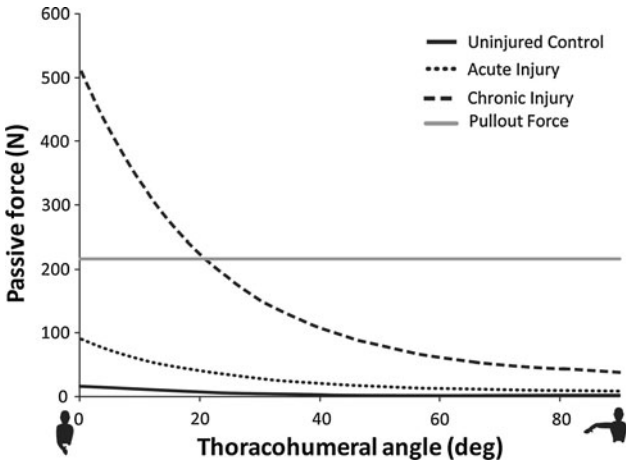

Fig. 4 Passive muscle–tendon unit tension after simulated acute and chronic rotator cuff tears. Simulation analysis was performed to study the passive tension during abduction developed by the muscle–tendon unit after rotator cuff tears for (1) uninjured control; (2) acute tear (simulated by 1.5 cm retraction); and (3) chronic tear (simulated by 3 cm retraction). A representative pullout strength of 215 N is indicated with a *grey line* and represents the passive force required for failure of suture and anchoring techniques used during rotator cuff repair surgery [10]. The chronic tear group is associated with increased passive forces, especially when the arm is adducted (smaller thoracohumeral angle). Passive forces predicted by the simulation analysis at 60 degrees abduction are consistent with observed intraoperative passive forces (0–45 N) [8] (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

of current anchor fixation methods. Furthermore, larger gap distances were found to be associated with reduced peak isometric moment-generating capacity, with reductions up to 53 % for simulated chronic rotator cuff tears (Fig. 5). This study elucidated the biomechanical consequences of repairs of large gap lengths in the rotator cuff and provided insight as to why repairs in the chronic tear setting are associated with poorer clinical outcomes [57]. Increased abduction of the arm used to reduce the supraspinatus tendon intraoperatively for the repair of larger gaps may ultimately lead to increased failure postoperatively during shoulder adduction. For larger tendon defects, the loss of strength in the supraspinatus may be substantial following repair, even if re-tearing is prevented.

Improvements for surgical rotator cuff repair

The experimental and computational studies described above point towards a need for treatment methods that reduce retraction, reduce high passive forces in the repaired

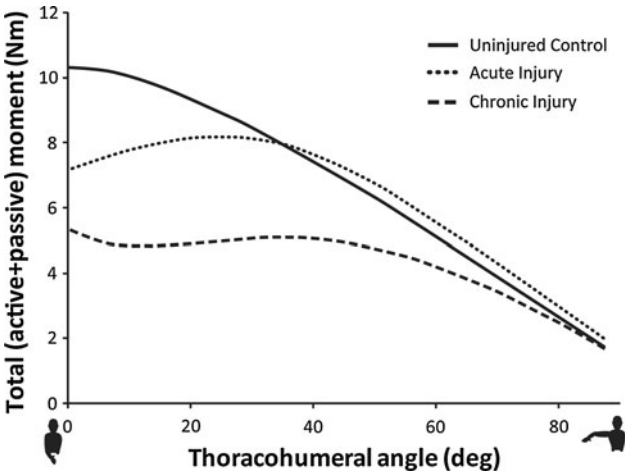

Fig. 5 Total (active plus passive) isometric moment-generating capacity after simulated acute and chronic rotator cuff tears. Function of the rotator cuff muscle–tendon unit is assessed after simulated repair. Throughout the abduction range of motion, simulation analysis was performed to study the active moment generating capacity developed by the muscle–tendon unit after rotator cuff tears for (1) uninjured control; (2) acute tear (simulated by 1.5 cm retraction); and (3) chronic tear (simulated by 3 cm retraction). Chronic tears, which are simulated by larger gap lengths, are associated with reduced peak isometric moment-generating capacity, with reductions up to 53 %. When repairing a chronically torn and retracted rotator cuff, total moment is affected by two mechanisms: (1) lengthening of the muscle results in less optimal actin–myosin cross-bridging and (2) the interaction between the force and moment arm profiles are altered (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

muscle–tendon unit, and improve healing of tendon to bone to reduce the re-tear risk and improve postoperative muscle function. Methods for reducing gap lengths, such as tendon grafts or graft substitutes, may limit the negative biomechanical consequences of the surgical repair of excessively retracted rotator cuff muscle–tendon units. Various materials such as human and animal skin, porcine small intestinal submucosa, muscle autografts and allografts, and synthetic materials reveal positive results for bridging large rotator cuff tear gaps and remain under investigation [12, 67]. Santoni et al. [56] used a polyurethane scaffold mesh to augment a repair of chronic rotator cuff tear in an ovine model. The mesh provided greater mechanical strength of the repair construct during the critical healing period compared control animals with suture anchor repair [56]. The application of acellular human dermal matrix allograft showed promising results at a minimum of 2-year follow-up and remains under investigation [66]. Further research in the area of scaffolds for bridging repairs of chronic rotator cuff repairs is needed.

Application of mesenchymal stem cells from bone marrow vents described as ‘crimson duvet’ has been propagated to enhance tendon-to-bone healing [59]. The mesenchymal stem cells and growth factors from the bone marrow may improve vascular supply to the repair site and promote healing. The use of transforming growth factor beta three (TGF-β3) during rotator cuff repair in an animal model showed improved structural and mechanical properties of the tendon-to-bone interface [45]. Rotator cuff tear repair in a sheep model using fibre wire sutures coated with recombinant human platelet derived growth factor revealed improved histological healing but similar load-to-failure testing properties compared to uncoated sutures [63]. These promising results warrant further research in the application of growth factors and cytokines to improve rotator cuff repairs.

A possible way to improve the manipulation of a torn rotator cuff tendon may be preoperative chemo denervation of the muscle–tendon unit with *Botulinum neurotoxin* A (BoNTA) [42, 44]. Muscle–tendon unit stiffness was decreased by 30 % in a rat gastrocnemius muscle 1 week following injection [42]. In the rat rotator cuff model, injection of BoNTA could pharmacologically modulate and reduce the elasticity of the in vivo viscoelastic muscle–tendon unit. The nervous system contributes to the in vivo passive biomechanical properties of repair tension experienced during rotator cuff repair [44]. Treatment of the rotator cuff with BoNTA prior to surgery may improve the surgical manipulation of the stiff and retracted tendon [42, 44], with the potential additional benefit of ‘bioprotecting’ the tendon-to-bone repair. By temporarily and reversibly weakening the muscle, the active contractile force is reduced and cannot cause rupture at the repair site [40]. However, recent reports in the rat rotator cuff model, in which ‘bioprotection’ of the repair site was employed, demonstrated either equivocal or reduced healing biomechanics at the tendon-to-bone junction [21, 33].

In a study by Galatz et al. [21], the complete removal of load on a repaired rotator cuff through the use of BoNTA and casting, resulted in weaker biomechanical behaviour at the tendon-to-bone insertion. These results indicate that some load is necessary to ensure improved supraspinatus healing after rotator cuff repair [21]. Hettrich et al. [33] demonstrated equivocal biomechanics strength at the tendon-to-bone junction between the BoNTA group and the control groups; however, BoNTA did result in decreased muscle weight presumably secondary to chemical paresis of the muscle and muscle atrophy. This change in muscle mass eventually was regained within the study time period of 24 weeks. Histologically, there was greater tendon-to-bone organization in the BoNTA protected group at the early time period of 4 weeks, when compared to traditional repair methods. Yet the authors caution that the rat model, which has rapid healing of the supraspinatus tendon after repair of rotator cuff tears, makes it difficult to comment on the clinical applicability of these results in humans [33]. Further studies are needed to investigate the clinical benefit

of BoNTA modulation of biomechanical stiffness and the potential for 'bioprotection' of the repair site.

Limitations for the use of animal models

The use of small animal models for studies of rotator cuff tear pathology has provided a fundamental understanding of the underlying molecular pathways of muscle atrophy and functional muscle impairment (Fig. 6). Larger animals (dog, sheep), non-human primates, and human cadaver studies have been used to confirm the findings in small animals and evaluate the novel repair techniques. While non-human primates are closer to human anatomy, their availability for translational studies of the rotator cuff is limited and the associated ethics should be considered

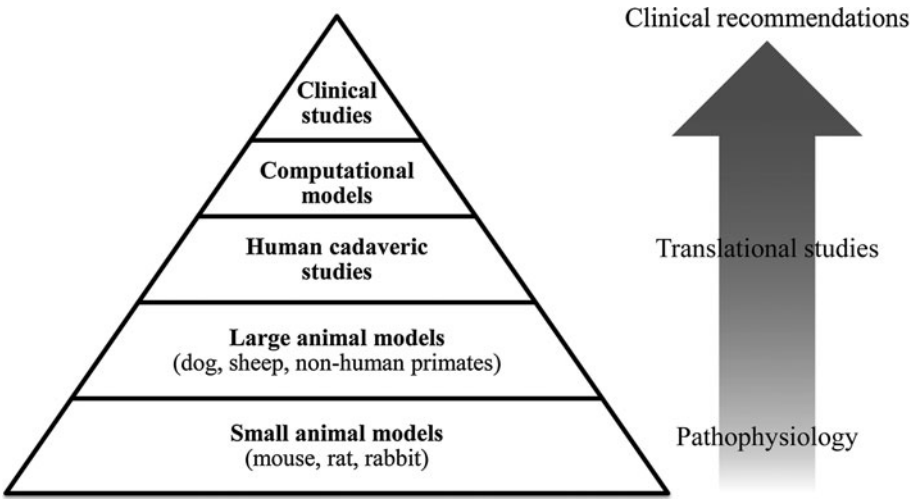

Fig. 6 The pathway from basic science animal studies to clinical recommendations. Rotator cuff research using small animal models has provided a solid foundation of the underlying pathophysiology of the disease and continues to be utilized for studies of molecular pathways and in vivo functional biomechanics. Studies in large animal models have confirmed the findings in small animals on a larger scale and deepened our understanding of muscular changes following rotator cuff tears with clinical implications. Human cadaveric studies have provided improved repair techniques, but in vivo functional assessment has been incomplete and difficult to characterize. Computational models may bridge the gap from large animal models and human cadaveric studies to clinical studies and provide clinical recommendations with the use of a mathematical framework based on human anatomic and physiologic data (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

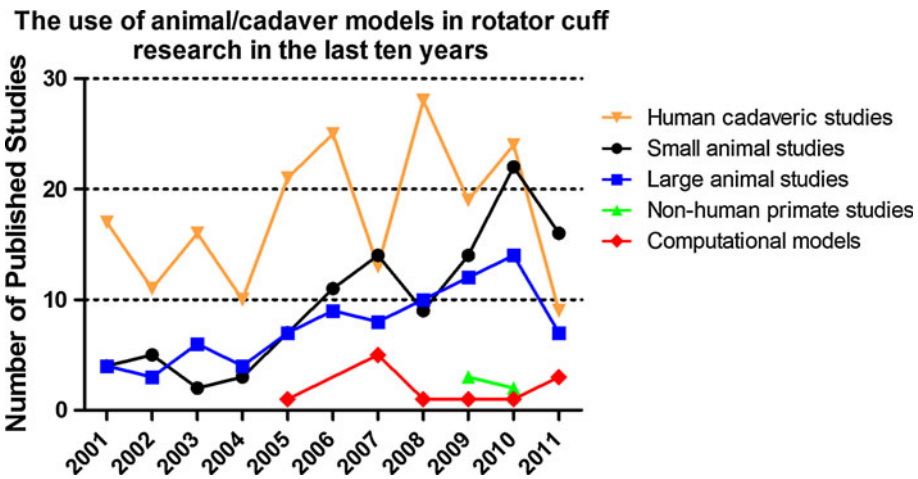

Fig. 7 In the last ten years of rotator cuff research, five non-human primate studies and twelve computational studies were conducted compared to 107 studies in small animals, 84 studies in large animals, and 193 human cadaveric studies. The use of small and large animal models for rotator cuff research has increased in the last ten years. Particularly, the introduction of the rat rotator cuff model has provided a valuable tool for molecular and functional rotator cuff research. While human cadaveric studies have been the mainstay for the research of repair techniques, non-human primates and computational models seem to be underutilized (Reproduced with permission from Koman LA ed. Wake Forest University Orthopaedic Workbook, Winston-Salem, Wake Forest University Orthopaedic Press 2012)

carefully. In addition, animal studies are inherently limited by the difference in scale and pathophysiology between animals and humans. While the findings from animal studies can provide a basic understanding of a disease process that may lead to novel hypotheses, further investigations are necessary to formulate definitive clinical recommendations [31]. The use of computational models in the study of rotator cuff pathology may bridge the gap from animal models and cadaver studies to clinical translation by providing a platform to further explore biomechanical aspects of rotator cuff tears and repair; this approach has been underutilized in the past.

In a search of the National Library of Congress (PubMed) for the keyword 'rotator cuff' limited to animal studies AND 'human cadaver' AND/OR 'computational model' from 2001 to 2011, 107 studies utilizing small animals were found (Fig. 7). Large animal models were used in 84 studies, non-human primates in five studies, and human cadaveric specimen in 193 studies. Computational modelling was used in only twelve studies of the rotator cuff during the last 10 years and represents an area of opportunity to advance rotator cuff research into clinical practice. Biomechanical data from the large number of human cadaveric studies could be imported into computational models of the human upper extremity for clinical integration and translation.

Conclusion

The complementary clinical experiments, animal model experiments, and computational simulations described in this report have provided a picture of the structural changes in muscle following rotator cuff injury and repair and the implications of these changes for function of the rotator cuff. The implications drawn from this collection of studies of rotator cuff pathology emphasize the importance of preventing permanent muscular changes with detrimental results. Chronically torn rotator cuff muscle–tendon units are characterized by increased fibrofatty infiltration and increased biomechanical stiffness (as verified in animal models); increased retraction in chronic rotator cuff tears can lead to increased repair tensions and a reduction in contractile muscle force of approximately 50 % in animal and simulation studies (Fig. 5). While the limitations of animal models need to be considered, earlier surgical intervention for patients with acute rotator cuff tears may improve clinical outcomes, because lower surgical repair tensions are necessary and fewer electromyographic neuromuscular changes are experienced [31, 43]. However, there is still insufficient information to guide the treatment of chronic rotator cuff tears, and this condition and the appropriate rehabilitation strategies require further research.

Acknowledgments This project is taken in part from a dissertation submitted to the Neuroscience Program, Wake Forest University Graduate School of Arts and Sciences, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The authors would like to thank Gary G. Poehling, MD for his helpful comments and suggestions.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Barton ER, Gimbel JA, Williams GR, Soslowsky LJ (2005) Rat supraspinatus muscle atrophy after tendon detachment. J Orhtop Res 23(2):259–265
2. Bedi A, Fox AJ, Harris PE, Deng XH, Ying L, Warren RF, Rodeo SA (2010) Diabetes mellitus impairs tendon-bone healing after rotator cuff repair. J Shoulder Elbow Surg 19(7):978–988
3. Bedi A, Fox AJ, Kovacevic D, Deng XH, Warren RF, Rodeo SA (2010) Doxycycline-mediated inhibition of matrix metalloproteinases improves healing after rotator cuff repair. Am J Sports Med 38(2):308–317
4. Bedi A, Kovacevic D, Hettrich C, Gulotta LV, Ehteshami JR, Warren RF, Rodeo SA (2010) The effect of matrix metalloproteinase inhibition on tendon-to-bone healing in a rotator cuff repair model. J Shoulder Elbow Surg 19(3):384–391
5. Bjorkenheim JM (1989) Structure and function of the rabbit's supraspinatus muscle after resection of its tendon. Acta Orthop Scand 60(4):461–463
6. Coleman SH, Fealy S, Ehteshami JR, MacGillivray JD, Altchek DW, Warren RF, Turner AS (2003) Chronic rotator cuff injury and repair model in sheep. J Bone Joint Surg Am 85-A(12):2391–2402
7. Costouros JG, Porramatikul M, Lie DT, Warner JJ (2007) Reversal of suprascapular neuropathy following arthroscopic repair of massive supraspinatus and infraspinatus rotator cuff tears. Arthroscopy 23(11):1152–1161
8. Davidson PA, Rivenburgh DW (2000) Rotator cuff repair tension as a determinant of functional outcome. J Shoulder Elbow Surg 9(6):502–506
9. de Groot JH, Brand R (2001) A three-dimensional regression model of the shoulder rhythm. Clin Biomech (Bristol, Avon) 16(9):735–743
10. Demirhan M, Atalar AC, Kilicoglu O (2003) Primary fixation strength of rotator cuff repair techniques: a comparative study. Arthroscopy 19(6):572–576
11. Derwin KA, Baker AR, Codsi MJ, Iannotti JP (2007) Assessment of the canine model of rotator cuff injury and repair. J Shoulder Elbow Surg 16(5 Suppl):S140–S148
12. Derwin KA, Badylak SF, Steinmann SP, Iannotti JP (2010) Extracellular matrix scaffold devices for rotator cuff repair. J Shoulder Elbow Surg 19(3):467–476
13. Fabis J, Kordek P, Bogucki A, Synder M, Kolczynska H (1998) Function of the rabbit supraspinatus muscle after detachment of its tendon from the greater tubercle. Observations up to 6 months. Acta Orthop Scand 69(6):570–574
14. Fabis J, Kordek P, Bogucki A, Mazanowska-Gajdowicz J (2000) Function of the rabbit supraspinatus muscle after large detachment of its tendon: 6-week, 3-month, and 6-month observation. J Shoulder Elbow Surg 9(3):211–216
15. Fabis J, Danilewicz M, Omulecka A (2001) Rabbit supraspinatus tendon detachment: effects of size and time after tenotomy on morphometric changes in the muscle. Acta Orthop Scand 72(3):282–286

16. Fealy S, Adler RS, Drakos MC, Kelly AM, Allen AA, Cordasco FA, Warren RF, O'Brien SJ (2006) Patterns of vascular and anatomical response after rotator cuff repair. Am J Sports Med 34(1):120–127
17. Frey E, Regenfelder F, Sussmann P, Zumstein M, Gerber C, Born W, Fuchs B (2009) Adipogenic and myogenic gene expression in rotator cuff muscle of the sheep after tendon tear. J Orthop Res 27(4):504–509
18. Fuchs B, Weishaupt D, Zanetti M, Hodler J, Gerber C (1999) Fatty degeneration of the muscles of the rotator cuff: assessment by computed tomography versus magnetic resonance imaging. J Shoulder Elbow Surg 8(6):599–605
19. Galatz L, Rothermich S, VanderPloeg K, Petersen B, Sandell L, Thomopoulos S (2007) Development of the supraspinatus tendon-to-bone insertion: localized expression of extracellular matrix and growth factor genes. J Orhtop Res 25(12):1621–1628
20. 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-A(2):219–224
21. Galatz LM, Charlton N, Das R, Kim HM, Havlioglu N, Thomopoulos S (2009) Complete removal of load is detrimental to rotator cuff healing. J Shoulder Elbow Surg 18(5):669–675
22. 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
23. Gerber C, Meyer DC, Schneeberger AG, Hoppeler H, von Rechenberg 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-A(9):1973–1982
24. Gerber C, Schneeberger AG, Hoppeler H, Meyer DC (2007) Correlation of atrophy and fatty infiltration on strength and integrity of rotator cuff repairs: a study in thirteen patients. J Shoulder Elbow Surg 16(6):691–696
25. Gerber C, Meyer DC, Nuss KM, Farshad M (2011) Anabolic steroids reduce muscle damage caused by rotator cuff tendon release in an experimental study in rabbits. J Bone Joint Surg Am 93(23):2189–2195
26. 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
27. 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
28. Gladstone JN, Bishop JY, Lo IK, Flatow EL (2007) 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 35(5):719–728
29. Goutallier D, Postel JM, Bernageau J, Lavau L, Voisin MC (1994) Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin Orthop Relat Res 304(304):78–83
30. Goutallier D, Postel JM, Gleyze P, Leguilloux P, Van Driessche S (2003) Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears. J Shoulder Elbow Surg 12(6):550–554
31. Gulotta LV (2011) Tension required to repair rotator cuff is detrimental to muscle function. J Bone Joint Surg Am 93(18):e110
32. Gupta R, Lee TQ (2007) Contributions of the different rabbit models to our understanding of rotator cuff pathology. J Shoulder Elbow Surg 16(5 Suppl):S149–S157
33. Hettrich CM, Rodeo SA, Hannafin JA, Ehteshami J, Shubin Stein BE (2011) The effect of muscle paralysis using Botox on the healing of tendon to bone in a rat model. J Shoulder Elbow Surg 20(5):688–697
34. Holzbaur KR, Murray WM, Delp SL (2005) A model of the upper extremity for simulating musculoskeletal surgery and analyzing neuromuscular control. Ann Biomed Eng 33(6):829–840
35. 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
36. Jamali AA, Afshar P, Abrams RA, Lieber RL (2002) Differential expression of neural cell adhesion molecule (NCAM) after tenotomy in rabbit skeletal muscle. J Orthop Res 20(2):364–369
37. Jozsa L, Kannus P, Thoring J, Reffy A, Jarvinen M, Kvist M (1990) The effect of tenotomy and immobilisation on intramuscular connective tissue. A morphometric and microscopic study in rat calf muscles. J Bone Joint Surg Br 72(2):293–297
38. Kim HM, Dahiya N, Teefey SA, Keener JD, Galatz LM, Yamaguchi K (2010) Relationship of tear size and location to fatty degeneration of the rotator cuff. J Bone Joint Surg Am 92(4):829–839
39. Ma CB, Comerford L, Wilson J, Puttlitz CM (2006) Biomechanical evaluation of arthroscopic rotator cuff repairs: double-row compared with single-row fixation. J Bone Joint Surg Am 88(2):403–410
40. Ma J, Shen J, Smith BP, Ritting A, Smith TL, Koman LA (2007) Bioprotection of tendon repair: adjunctive use of botulinum toxin A in Achilles tendon repair in the rat. J Bone Joint Surg Am 89(10):2241–2249
41. Mallon WJ, Wilson RJ, Basamania CJ (2006) The association of suprascapular neuropathy with massive rotator cuff tears: a preliminary report. J Shoulder Elbow Surg 15(4):395–398
42. 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
43. 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
44. Mannava S, Wiggins WF, Saul KR, Stitzel JD, Smith BP, Koman LA, Smith TL, Tuohy CJ (2011) Contributions of neural tone to in vivo passive muscle-tendon unit biomechanical properties in a rat rotator cuff animal model. Ann Biomed Eng 39(7):1914–1924
45. Manning CN, Kim HM, Sakiyama-Elbert S, Galatz LM, Havlioglu N, Thomopoulos S (2011) Sustained delivery of transforming growth factor beta three enhances tendon-to-bone healing in a rat model. J Orthop Res 29(7):1099–1105
46. Matsumoto F, Uhthoff HK, Trudel G, 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
47. 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
48. Meyer DC, Hoppeler H, von Rechenberg B, Gerber C (2004) A pathomechanical concept explains muscle loss and fatty muscular changes following surgical tendon release. J Orthop Res 22(5):1004–1007
49. Meyer DC, Gerber C, Von Rechenberg B, Wirth SH, Farshad M (2011) Amplitude and strength of muscle contraction are reduced in experimental tears of the rotator cuff. Am J Sports Med 39(7):1456–1461
50. Oh JH, Kim SH, Ji HM, Jo KH, Bin SW, Gong HS (2009) Prognostic factors affecting anatomic outcome of rotator cuff

repair and correlation with functional outcome. Arthroscopy 25(1):30–39
51. 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
52. 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
53. Rowshan K, Hadley S, Pham K, Caiozzo V, Lee TQ, Gupta R (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
54. Rubino LJ, Sprott DC, Stills HF Jr, Crosby LA (2008) Fatty infiltration does not progress after rotator cuff repair in a rabbit model. Arthroscopy 24(8):936–940
55. Safran O, Derwin KA, Powell K, Iannotti JP (2005) Changes in rotator cuff muscle volume, fat content, and passive mechanics after chronic detachment in a canine model. J Bone Joint Surg Am 87(12):2662–2670
56. Santoni BG, McGilvray KC, Lyons AS, Bansal M, Turner AS, Macgillivray JD, Coleman SH, Puttlitz CM (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
57. Saul KR, Hayon S, Smith TL, Tuohy CJ, Mannava S (2011) Postural dependence of passive tension in the supraspinatus following rotator cuff repair: a simulation analysis. Clin Biomech (Bristol, Avon) 26(8):804–810
58. Schmutz S, Fuchs T, Regenfelder F, Steinmann P, Zumstein M, Fuchs B (2009) Expression of atrophy mRNA relates to tendon tear size in supraspinatus muscle. Clin Orthop Relat Res 467(2):457–464
59. Snyder SJ, Burns J (2009) Rotator cuff healing and the bone marrow "Crimson Duvet" from clinical observations to science. Tech Shoulder Elbow Surg 10(4):130–137
60. Sonnabend DH, Howlett CR, Young AA (2010) Histological evaluation of repair of the rotator cuff in a primate model. J Bone Joint Surg Br 92(4):586–594
61. Soslowsky LJ, Thomopoulos S, Tun S, Flanagan CL, Keefer CC, Mostow J, Carpenter JE (2000) Neer award 1999. Overuse activity injures the supraspinatus tendon in an animal model: a histologic and biomechanical study. J Shoulder Elbow Surg 9(2):79–84
62. 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
63. Uggen C, Dines J, McGarry M, Grande D, Lee T, Limpisvasti O (2010) The effect of recombinant human platelet-derived growth factor BB-coated sutures on rotator cuff healing in a sheep model. Arthroscopy 26(11):1456–1462
64. Uhthoff 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
65. Vitale MA, Vitale MG, Zivin JG, Braman JP, Bigliani LU, Flatow EL (2007) Rotator cuff repair: an analysis of utility scores and cost-effectiveness. J Shoulder Elbow Surg 16(2):181–187
66. Wong I, Burns J, Snyder S (2010) Arthroscopic GraftJacket repair of rotator cuff tears. J Shoulder Elbow Surg 19(2 Suppl):104–109
67. Yadav H, Nho S, Romeo A, MacGillivray JD (2009) Rotator cuff tears: pathology and repair. Knee Surg Sports Traumatol Arthrosc 17(4):409–421
68. Zajac FE (1989) Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. Crit Rev Biomed Eng 17(4):359–411