General

Pharmacologic Enhancement of Rotator Cuff Repair: A Narrative Review

Maksim Vaysman[1] [a], Matthew Alben[2], Matthew Todd[3], Charles Ruotolo[1]

[1] Orthopedic Surgery, Nassau University Medical Center, [2] Orthopedic Surgery, Nassau University Medical Center; Osteopathic Medicine, New York Institute of Technology, [3] Orthopedic Surgery, Nassau University Medical Center; Osteopathic Medicine, Des Moines College of Osteopathic Medicine

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Introduction

As rotator cuff repairs (RCRs) are among the most common procedures in upper extremity orthopedics, healing augmentation using pharmacologic enhancement of the repaired rotator cuff muscle is of particular interest.

Objective

The purpose of this study is to review the current understanding of Matrix Metalloproteinases (MMPs), Doxycycline, Testosterone, Estrogen, Growth hormone/ IGF-1, Vitamin D, and Vitamin C as a means to mitigate deleterious effects and propagate factors that support healing following RCR.

Methods

A review of English language articles in PubMed and Medline was conducted in December of 2020. All articles describing the current understanding of the aforementioned therapies were reviewed. Studies were excluded if they were non-English or reported incomplete results.

Results

Matrix metalloproteinases (MMP's) are fundamental to the healing process after rotator cuff tears through a delicate balance of various proteases that can be modulated by doxycycline through inhibition. While testosterone has shown to induce replication and differentiation of the tendon stem-cells, estrogen agonists have been shown to decrease inflammation and muscle atrophy. Though growth hormone being associated with elevated collagen synthesis and decreased anoxic damage when present, clinical studies have shown inconclusive and adverse effects on rotator cuff healing. Patients with Vitamin D deficiency have shown to have increased fatty infiltration in rotator cuff muscle while Vitamin C functions as an antioxidant that increases collagen and fibroblast proliferation.

Conclusion

As manipulation of pharmacologic factors shows potential for enhancing healing following RCRs, future studies are needed to establish a viable augmentation strategy to improve patient outcomes

a **Corresponding author:**
Maksim Vaysman, DO
Address: 2201 Hempstead Turnpike, East Meadow, NY 11554.
Email: maxvaysman@gmail.com
Phone: 631-332-8165

BACKGROUND

Despite advancements in the treatment of rotator cuff tears (RCTs) over the past several decades, RCTs are among the most common and painful shoulder pathologies in upper extremity orthopedics. Full-thickness tears have been reported in 25% of those over the age of 60 and in 50% of people in their 80's; as such, those requiring surgical treatment may be subject to revision with rates reported at 8.38%.[1,2] As poor healing has been attributed to roughly 85% of failures within the first six months following repair, pharmacologically enhancing the underlying pathophysiology of healing is of particular interest.

Musculo-tendinous changes that occur in response to trauma with subsequent degeneration of the tendon-bone insertion site are dependent on the underlying biology at the repair site. The insertion site of the rotator cuff, a specialized fibrocartilaginous structure known as the enthesis, is divided into four respective zones: tendon proper, unmineralized fibrocartilage, mineralized fibrocartilage, and bone.[1,3] At the time of injury, muscle retraction occurs in conjunction with degenerative changes in the enthesis which is worsened by the chronicity of the condition. Healing of the tendon then occurs through a three stage process of inflammation (first week), fibroblast infiltration (48 hours to 8 weeks), and a remodeling phase.[1,3,4]

Inflammatory cell migration induces muscle fiber apoptosis, retraction, and atrophy with eventual myogenic precursor cell shift into the adipogenic pathway for fatty infiltration.[5] Fibroblast infiltration leads to fibrovascular scar tissue with increased type three collagen and decreased capillary density at the tendon-bone insertion site, further limiting progenitor cell recruitment with eventual contraction of the collagen-based scar tissue.[6] As the remodeling phase progresses, collagen fibers resembling those of the Sharpey's fibers that connect the tendon to periosteum appear around 12 weeks with continuity between collagen fibers observed at 26 weeks.[7] Ultimately, the tissue organizes into a biomechanically inferior tendon-bone interface predisposed to a retear.[1,3,4]

The purpose of this study is to review the current understanding of Matrix Metalloproteinases (MMPs), Doxycycline, Testosterone, Estrogen, Growth hormone/ IGF-1, Vitamin D, and Vitamin C as a means to mitigate deleterious effects and propagate factors that support healing following RCR.

METHODS

A narrative review was conducted via a comprehensive literature search in PubMEd and Medline utilizing a combination of key words and MeSH terms. Key words consisted of Rotator Cuff, RCR, Pharmacologic, Biologic, MMP, Matrix Metalloproteinases, Doxycycline, Estrogen, Growth Hormone, Vitamin D, and Vitamin C. Three co-authors independently reviewed and extracted the relevant data from the articles of interest concerning pharmacological enhancement of rotator cuff healing. Results were limited to English language articles with complete results. Any conflicts with inclusion or exclusion during article selection were ultimately resolved by the senior author.

REVIEW

MMP

Matrix metalloproteinases (MMPs) are known to be involved in the remodeling and degradation of the extracellular matrix (ECM) during chronic RCTs, but their mechanism of action and role following an acute injury has been reported on more recently (Table 1). MMPs belong to a family of 24 zinc-dependent endopeptidases that become active after proteolysis of an inactive proform and have a variety of cellular functions including cell proliferation, migration, and differentiation.[5] The tissue inhibitors of metalloproteinase (TIMPs) are the natural endogenous inhibitors of the MMPs, and together, play an essential role in the tissue remodeling that occurs during rotator cuff tendon healing. MMPs degrade all components of the extracellular matrix once activated by proteolytic cleavage, with MMP-3 being a key player by activating other MMPs in this manner.[8]

TIMP-1 is not present in normal tendons, but has increased expression after acute tears and may serve as an early marker of ECM remodeling.[9] Rotator cuff muscle is composed primarily of type one collagen, however after injury there is a shift in the ratio of type one to type three collagen.[9,10] Since type three collagen is normally formed in the early stages of healing with MMP-13 having been shown to efficiently degrade type one collagen, this shift illustrates a transition in metabolism towards matrix degradation with MMPs playing a key role in rotator cuff healing after tearing.[10,11]

Studies have shown significantly increased levels of collagenase-3 (MMP-13) mRNA levels, as well as a decrease in stromelysin-1 (MMP-3) and TIMP-2, -3, and -4 mRNA levels after RCTs.[10] This has been corroborated by western blotting demonstrating an increase in the active form of collagenase-3 (MMP-13) after acute injury.[10] As these enzymes have been found at both the site of injury and healthy tissue, repeated mechanical stresses with an altered interaction between tenocytes and the ECM may produce a more global change in their local concentrations.[9] As such, a positive feedback loop of a failed healing response may ensue, predisposing the tendon further injury as changes reflect a more chronic tendinopathy.[9] Samples from patients with RCTs showed higher levels of these proteins when compared with those with other shoulder pathology, such as subacromial impingement syndrome. When such pathologies occur concomitantly with RCTs, this may further exacerbate the underlying biologic response and support the theory of progressive failure of the rotator cuff.[11]

After RCTs the muscles undergo degenerative changes of fatty infiltration and muscle atrophy, which is associated with worse outcomes after RCR. Muscle fatty infiltration occurs as a combination of fat progenitor cells migrating into the muscle following injury and resident muscle multipotent progenitor cell differentiation with both mechanisms receiving cues from the ECM via paracrine signaling pathways. MMP-13 knockout mice have a significant increase in the amount of fatty infiltration in compared to

Table 1. MMP

Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Liu et al, 2017[5]	9 MMP-13 (-/-) knockout mice 9 MMP-13 (+/+) wildtype mice	Unilateral complete transection of the supra-/infra-spinatus and suprascapular nerve Mice were sacrificed 6 weeks post-op	Transected muscles were harvested for histology and gene expression via RT-PCR	No significant difference in muscle atrophy or fibrosis Knock-out mice had a significant increase in expression of fatty infiltration related genes	Muscle fatty infiltration is due to a combination of fat progenitor cell migration and resident muscle multipotent progenitor cell differentiation
Garofalo et al, 2011[8]	Meta-analysis	-	-	-	-
Castagna et al, 2013[9]	13 patients undergoing arthroscopic repair of rotator cuff tear	Supraspinatus biopsy specimens harvested in bloc from intact middle portion of tendon more than 1 cm from torn edge, from the lateral edge of the tear, and from the superior one third of the macroscopically intact subscapularis tendon used as control	Significantly greater fibrocartilage seen at healing enthesis (P < .05), significantly greater collagen organization (P <.01), and a significant reduction in collagen degradation in the A2 M-treated animals compared with controls at 2 weeks (P < .05).	Local delivery of MMP inhibitor resulted in distinct histologic differences at the tendon-to-bone interface after rotator cuff repair	Local delivery of MMP inhibitor in perioperative period may result in a more mature, organized tendon-to-bone interface
Lo et al, 2004[10]	10 patients undergoing RC repair for full thickness tears; Tissue also taken from cadaveric specimens with no gross evidence of rotator cuff pathology	10 patients undergoing rotator cuff repair had full-thickness rotator cuff tears	Histological evidence of tendinopathy present in patients with tear of rotator cuff and not in the macroscopically intact subscapularis tendon	Significant increase in MMP 1, MMP 2, MMP 3, TIMP-1, and TIMP-2 levels in all examined specimens including intact portion of supraspinatus tendon and control specimens	Seemingly intact portions of rotator cuff tendon can present with tendinopathic features and altered cellular metabolism
Sejersen et al, 2015[11]	Systematic review of literature between January 1, 1990 and 18 December 18, 2012 in PubMed, Embase, and Web of Science; 2199 studies identified with 54 included; 25 focused on rotator cuff or biceps tendinopathy	Most of the studies included quantified prespecified mRNA molecules and proteins using PCR and immunoassays	Simultaneous quantification of a limited number of prespecified	Tendency towards increase in collagen I and III, MMP-1, -9, and -13, TIMP-1, VEGF, and a decrease in MMP-3	Proteomics technologies may be a way to identify protein profiles thar characterize specific tendon disorders

the wild types.[5] Ultimately, MMPs and TIMPs play a vital role in ECM remodeling after RCR at the levels of mRNA transcription, proteolytic cleavage, protein expression, and paracrine signaling.

DOXYCYCLINE

Doxycycline, a potent tetracycline antibiotic, has long been used in the treatment of conditions such as acne, pneumonia, and Lyme disease, but its implications in RCR has more

Table 2. Doxycycline

Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Garofalo et al, 2011[8]	Meta-analysis	-	-	-	-
Bedi, 2010[12]	62 male Sprague-Dawley rats: - 31 control supraspinatus repair - 31 experimental with alpha-2 macroglobulin protein [MMP inhibitor] with identical surgical repair	alpha-2 macroglobulin (A2 M), a universal MMP inhibitor applied to tendon-bone interface before surgical repair	Significantly greater fibrocartilage seen at healing enthesis (P < .05), significantly greater collagen organization (P <.01), and a significant reduction in collagen degradation in the A2 M-treated animals compared with controls at 2 weeks (P < .05).	Local delivery of MMP inhibitor resulted in distinct histologic differences at the tendon-to-bone interface after RCR	Local delivery of MMP inhibitor in perioperative period may result in a more mature, organized tendon-to-bone interface
Rooney, 2018[13]	165 adult male Sprague-Dawley rats divided into cage activity or exercise groups, and further subdivided into acute and chronic study designs	The rats were divided into cage activity or exercise therapy consisting of graduated treadmill training and flat treadmill exercise sessions. Half the rats additionally received 10 mg/kg of doxycycline orally every 24 hours functioning as a MMP inhibitor	Assays included supraspinatus tendon mechanics and histology and muscle fiber morphologic and type analysis	Doxycycline improved tendon mechanical properties and collagen organization among chronic cage activity group, which was not consistently present in exercised groups. Combined with exercise, doxycycline also decreased average muscle fiber cross-sectional area.	These results suggest that administration of doxycycline can induce beneficial supraspinatus tendon adaptations without negatively affecting the muscle in caged activity animals, but may not be advantageous when combined with activity
Pasternack, 2006[14]	60 Sprague Dawley rate had their achilles tendons transected transversely	Doxycycline treatment of 130 mg/kg body weight/ day	Mechanical evaluation of achilles tendons at 5, 8, and 14 days	Decreased force of failure (p < 0.005) and energy uptake (p < 0.001) in doxycycline treated group	Doxycycline serum concentration was clinically relevant at 3.4 (SD 1.0) microg/ml

recently become a topic of interest (Table 2). This is due to recognition of the antibiotics direct and indirect role in metabolism. Doxycycline has shown broad spectrum inhibition of MMP-1, -2, -7, -8, -9, -12, and -13. In conjunction with zinc-binding inhibition, recent studies have shown a reduction of MMPs at the level of gene expression, diminished activation through the inflammatory cascade, and fewer reactive oxygen species.[8] By having the ability to modulate endogenous MMP activity to basal levels, doxycycline can be explored for reducing excessive degradation or remodeling after RCR.

A study by Bedi et al showed that doxycycline-treated caged mice had altered supraspinatus properties after RCR.[12] Through inhibition of MMP-13 perioperatively, doxycycline favorably influenced early healing of RCR by improving collagen organization, increased fibrocartilage, and greater strength of the healing enthesis.[12] Chronic doxycycline administration has been reported to increase tendon mechanics (stiffness, modulus, max load, max stress, and dynamic modulus).[13,15] However, doxycycline treatment following achilles tendon transection revealed a decrease in both force to failure (p < 0.005) and energy uptake (p < 0.001).[14] As MMP activity can vary throughout the remodeling process following injury, future studies are required to fully optimize and establish the clinical applicability of doxycycline use after RCR.

HORMONES: TESTOSTERONE

Testosterone and its metabolites have been studied in regards to their effect on musculoskeletal pathologies (Table 3). Khalkhali-Ellis et al reported that tendons contain receptors that are specific for testosterone, suggesting a potential role for testosterone to be used as a pharmacologic aid in tendon healing.[16] Denaro et al performed an in vitro study on healthy male supraspinatus tendons where the investigators progressively increased dihydrotestosterone (DHT) concentrations.[17] Their study showed that after 48

and 72 hours, the cultured cells had an increase in cell number as well as a more de-differentiated shape.[17] By regulating tendon stem cells, DHT may have potential in aiding healing of a RCT. However, using testosterone in a healthy tendon can contribute to tendinopathy and abnormalities as seen in anabolic steroid abuse.[17]

Wieser et al performed a study on chronically retracted RCTs in sheep.[18] The authors looked at mechano-pharmacologic stimulation of the infraspinatus by observing continuously lengthening the tendon with or without the addition of testosterone and growth hormone (GH). They found that the continuous lengthening helped restore some of the normal tendon anatomy, but neither testosterone or GH had a positive or negative effect. These studies suggest that there may be potential for testosterone supplementation to aid in rotator cuff healing, but more research is warranted in order to indicate a possible clinical application following RCR.

HORMONES: ESTROGEN

Estrogen has been known as a regulating factor of metabolism, but its role in healing and connective tissue injury resistance has been recently studied (Table 3). Produced from cholesterol in a series of reactions, it's final conversion from testosterone to estradiol by the enzyme aromatase. Estrogen exists in multiple forms with the most prevalent estrogen being 17β-estradiol and in smaller amounts as estrone and estriol. As a steroidal hormone, estrogen can freely pass through the plasma membrane and move into the nucleus where it can bind to its nuclear receptors, estrogen receptors α and β, to modify gene expression. These receptors are present in all musculoskeletal tissues, including muscle, bone, and tendon. Working concomitantly with Vitamin D, 17β-estradiol has been shown to upregulate Vitamin-D receptor (VDR) expression while administration of female sex and calciotropic hormone results in tendon-derived cell proliferation.[19]

When exposed to estrogen, rodents have shown a reduction in muscle damage and muscle cell membrane disruption following potentially injurious exercises.[20] When comparing ovariectomized rodents with and without estrogen therapy, those with replacement had reduced creatine-kinase release from muscle, decreased disruption of muscle structural proteins dystrophin and desmin, and diminished activation of lysosomal enzymes.[20] In respect to rotator cuff muscles, Tanaka et al compared supraspinatus healing after detachment and immediate repair of rats with and without ovariectomy.[21] They reported greater chondroid tissue, collagen organization, ultimate load to failure, ultimate stress, and bone mineral density in the control group while those with ovariectomy had poorer tendon insertion at the repair site with greater protease expression.[21]

Estrogen functions as an antioxidant, membrane stabilizer, and can attenuate the inflammatory response by mitigating muscle infiltration by leukocytes, such as neutrophils and macrophages.[20] Tamoxifen is a first generation selective estrogen receptor modulator (SERM) that acts as a competitive inhibitor for estrogen receptors, but has pro-estrogenic activity on bone and muscle. Similarly, tamoxifen has beneficial actions of scavenging peroxyl radicals, stabilizing biological membranes, preventing apoptosis, inhibiting fibrosis, and modulating calcium homeostasis.[22] Animal models treated with tamoxifen following chronic RCTs showed decreased muscle atrophy and inflammatory changes, with no apparent effect on adipogenesis.[22] Future studies are required to determine if the poor healing of a RCT in an estrogen deficient state is from the loss of the hormone alone or the net loss of synergistic effects with other factors, such as Vitamin D.

HORMONES: GROWTH HORMONE/IGF-1

GH has long been studied in regards to the muscle-tendon relationship and its potential use on tendon healing (Table 3). Both human and animal studies have reported an increase in collagen mRNA expression and fractional synthesis rate (FSR) in states of GH excess states.[23,24] Furthermore, cell death is decreased when insulin-like growth factor-1 (IGF-1) activates the PI3K signaling pathway and suggests that IGF-1 is a survival factor in tendon cells.[25]

Roughly 70-80% of IGF-1 in the blood circulates as complexes bound to several different proteins while only ~ 2% is the free form of IGF-1.[26] Though GH can act through several mechanisms (endocrine, paracrine, and autocrine), its effect on tendons via a systemic or local level has been of particular interest. Studies by Olesen et al and Nindl et al showed that exercise resulted in higher local concentrations of IGF-1 with concentrations greater than systemic levels.[29,30] While these findings allude to potential for GH use in direct tendon healing, in vivo studies by Baumgarten et al and Oh et al have respectively shown detrimental effects on rats and insignificant effects on humans with RCRs.[27,28]

Baumgarten et al carried out a two cohort treatment study on rats who underwent repair of acute RCTs.[27] The first cohort (n= 72) received postoperative treatment of placebo or subcutaneous GH at doses ranging between 0.1 to 10 mg/kg/day while the second cohort (n= 24) underwent either placebo or seven days preoperatively and twenty eight days postoperatively of 5 ml/kg of GH. The first cohort showed no difference upon mechanical testing while the second cohort showed worse force to failure more commonly at the bone itself than the tendon-bone interface of GH treated rats (21.1 +/- 5.85 versus 26.3 +/- 5.47 N, $p = 0.04$) of this cohort.[27] Oh et al carried out a randomized control trial in seventy-six patients who underwent arthroscopic RCR divided into a control group and two recombinant GH treated groups (4mg and 8 mg).[28] No difference in outcomes were found in the respective control, 4mg GH, and 8 mg GH groups when comparing healing failure rate (34.6%, 30.8%, 16.7%; $p > 0.05$), Goutallier grade of 3 or greater (34.6%, 23.2%, 20.8%; $p > 0.05$) or increased peak IGF-1 levels (186.31 ng/mL, 196.82 ng/mL, 279.43 ng/mL).[28] When comparing clinical outcomes, no difference was reported in respect to patient reported outcome measures, range of motion, pain visual analog scale ($p > 0.05$).[28] Though the study was limited by its sample size to produce significant results, the preliminary results warrant further investigation on the feasibility of GH treatment following RCR.

Table 3. Hormones

Testosterone					
Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Khalkhali-Ellis, 2002[16]	Molecular analysis study of synoviocytes in conjunction with ELISA and multiprobe ribonuclease protection assay	-	Synoviocytes were analyzed for the presence of androgen receptors and the effect of dihydrotestosterone and 17beta-estradiol, respectively, on interleukin 1beta induced expression of IL-6 and related cytokines in synoviocytes	- androgen receptors are present in synoviocytes - dihydrotestosterone inhibits interleukin 1beta induced IL-6, macrophage-colony stimulating factor, and granulocyte colony stimulating factor; while 17beta-estradiol at high concentrations induces these cytokines	-
Denaro, 2010[17]	Harvested tendon tissue blocks from supraspinatus tendons of 3 healthy male patients	The tissue blocks were used as explants for primary cell cultures and seeded into culture plates and incubated for 24 hours. Then DHT or Dulbecco's modified Eagle's medium (DHEM) only [control] were added to the culture plates	Cell morphology assessment and cell proliferation tests were performed at 48, 72, and 96 hours after DHT treatment	DHT treated tenocytes showed an increased proliferation rate at DHT concentrations higher than 10−8 M. Differences in cell numbers between control and DHT-treated cells were statistically significant ($P < 0.05$) after 48 and 72 hours of treatment.	In vitro, progressive increasing concentration of DHT at doses greater than 10−8 M had direct effects on male human tenocytes including increasing cell number.
Wieser, 2015[18]	Musculotendinous unit of infraspinatus tendon in 20 sheep	The retracted musculotendinous unit was subjected to continuous traction either with anabolic steroids group/insulin-like growth factor group or without (control group) over the course of 6 weeks	A new degeneration score for tendinous tissues, based on established knowledge of histological changes associated with tissue degeneration, was used for histological analysis at the time of tendon release, at the beginning of continuous re-lengthening and at repair in all animals	The new degeneration score for tendinous tissues improved from 15.5 (SD 1.3) points before to 9.8 (SC 3.8) points after re-lengthening and improved in a qualitatively and quantitatively similar fashion with pharmacologic stimulation. The steroid group improved from 13.7 (SD 1.6) to 9.8 (SD 1.9) and the IGF group from 13.3 (SD 3.6) to 8.8 (SD 1.8) points.	Mechanical stimulation significantly reduced tissue degeneration but the addition of pharmacologic stimulation had neither a measurable positive or negative impact on the degenerative process.

Estrogen					
Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Maman, 2016[19]	10 week old male Wistar rats with 3	Tendon derived cells from rat supraspinatus	- cell proliferation - mRNA expression of	Estradiol 17beta, Biochanin A, raloxifene, and Vitamin D significantly	Significant tendon derived cells proliferation can be achieved with

	rats for each experimental condition	were treated with Estradiol-17beta, Soy Isoflavones, raloxifene and estrogen receptors alpha and beta agonists and antagonists, less-calcemic Vitamin D analog, PTH, and vehicle control for 24 hours	estrogen receptor alpha and beta, Vitamin D receptor, scleraxis and collagen 1	increased tendon derived cell proliferation. Estrogen receptor alpha antagonists neutralized tendon derived cells respond to estradiol 17beta. Scleraxis expression decreased following estradiol 17beta and Vitamin D treatments.	commonly prescribed female sex and calciotropic hormones
Tiidus, 2011[20]	-	-	-	-	Recent research which documents the positive effects of estrogen and hormone replacement therapy on skeletal muscle mass, damage, and repair indices and force generation in older females. Discusses human and animal studies which outline further evidence for and potential mechanisms of the positive effects of estrogen on skeletal mass. Concludes with a brief overview of the overall health implications of HRT in aging females.
Tanaka, 2019[21]	48 adult female Sprague Dawley rats underwent detachment and immediate repair of the supraspinatus tendon at 17 weeks of age	24 underwent ovariectomy immediately before tendon detachment ad 24 age-matched non-ovariectomized rats were used as a control group	The repaired tendon-to-bone interface was evaluated in both groups at 2,4, 8, and 12 weeks after surgery utilizing micro-CT for their biomechanical properties, tissue histology, immunohistochemical staining, and osteoclast activity at the attachment sites.	Bone mineral density was significantly lower both at the insertion site and in cancellous area in the ovariectomized group than in the control group at weeks 2 to 12. Ultimate load to failure, ultimate stress, linear stiffness, and the Young modulus was also significantly lower in the ovariectomized group than in the control group at 2 and 4 weeks, but the difference was no longer significant at 8 and 12 weeks.	The estrogen deficient state after ovariectomy lead to decreased biomechanical properties and poor development of chondroid tissue compared with control rats, which influenced the repair of the tendon insertion after surgery
Cho, 2015[22]	16 male Jax C57BL/6J mice 24 weeks old at the time of surgery	The mice were randomly divided into Tamoxifen diet and Regular diet groups and then subjected to surgical creation of a large rotator cuff tear and suprascapular nerve transection in their left shoulder with the right shoulder	The muscles harvested from three randomly chosen mice from each each group were used for histological imaging, while those from the remaining five mice were used for RT-PCR analysis. Muscle weight, food intake, body mass, lean body percentage, and fat percentage were compared	While the tamoxifen fed group maintained their initial body weight and body composition throughout the experimental period, the regular diet fed group showed a gradual increase of body weight and fat percentage as well as a gradual decrease of lean body percentage.	Histology showed substantially decreased atrophy and endomysial inflammation in the Tamoxifen group, but no significant differences in the amount of intramuscular adipocytes and lipid droplets compared to the regular group

		serving as a control	between groups		

Growth Hormone					
Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Doessing, 2010[23]	18 male patients, 9 with acromegaly and nine with growth hormone deficiency. None healthy age matched male participants were included as controls.	Disproportionate growth of musculoskeletal tissue in both acromegalic and growth hormone deficient patients	Collagen mRNA expression and collagen protein fractional synthesis rate were determined locally in skeletal muscle and tendon in the nine acromegaly patients and the nine growth hormone	A higher expression for collagen and IGF1 mRNA in local musculotendinous tissue was observed in acromegaly patients relative to growth hormone deficient patients.	The results indicate a collagen stimulating role of local IGF1 in human connective tissue
Nielsen, 2014[24]	5 classical Ehlers-Danlos patients who met all three diagnostic criteria. Each patient was individually matched with two healthy controls on sex, age, BMI, and self-reported physical activity level.	0.1 mL of Recombinant human IGF-1 was injected into one patellar tendon of all participants at 24 and 6 hours before tendon biopsies were obtained. The contralateral tendon was injected at the same time points with an identical volume of isotonic saline.	The fractional synthesis rate of proteins in skin and tendon were measured with the stable isotope technique using a flood-primed continuous infusion over 6 hours.	Similar baseline FSR values in skin and tendon in the cEDS patients and controls [skin: 0.005 ± 0.002 (cEDS) and 0.007 ± 0.002 (CTRL); tendon: 0.008 ± 0.001 (cEDS) and 0.009 ± 0.002 (CTRL) %/h, mean ± SE]. IGF-1 injections significantly increased fractional synthesis rate values in classic Ehlers-Danlos patients but not in controls (delta values: cEDS 0.007 +/- 0.002, CTRL 0.001 +/- 0.001%/h)	Baseline protein synthesis rates in connective tissue appeared normal in cEFS patients and the patients responded with an increased tendon protein synthesis rate to IGF-1 injections
Scott, 2005[25]	Achilles tendon cell apoptosis prevention in the setting of hypoxia by IGF-I	- cells were cultured in an anaerobic chamber - cell death determined by flow cytometry - caspase activity determined by fluorometric assay - nuclear morphology examined via Hoechst staining	- effect of oxygen withdrawal on the viability of achilles tendon cells - ability of IGF-I to prevent achilles tendon cell death	Apoptosis inhibited by IGF-I exposure in a dose-dependent manner	IGF-I activates the pro-survival PKB pathway in achilles tendon cells
Gatti, 2012[26]	-	-	-	-	Review on the IGF/IGFFB system and it's relation to physical exercise
Baumgarten, 2013[27]	96 rats underwent acute rotator cuff injuries and were	Protocol one of 72 rats: - divided into groups of	- ultimate stress - ultimate force - stiffness	- Protocol one showed no significant difference in the outcome of interest - Protocol 2 had significantly worse	Failure in the protocol two group was more likely to occur through the tendon-bone interface

	separated into two protocol groups	placebo, and human growth hormone at 0.1, 1, 2, 5, and 10 mg/kg/day Protocol two of 24 rats: - placebo group - subcutaneous dosage of 5 mg/kg twice per day preoperatively for seven days and twenty-eight days postoperatively	- energy to failure - ultimate distension	ultimate force to failure in the growth hormone group	
Oh et al, 2018[28]	76 patients who underwent arthroscopic rotator cuff repair	Treatment groups received once weekly subcutaneous growth hormone for 3 months; groups were divided as: - placebo group, n of 26 - 4 mg group, n of 26 - 8 mg group, n of 26	- healing failure rate - proportion of severe fatty infiltration - functional outcomes - range of motion - pain visual analog scale - peaked insulin-like growth factor-1 level	All values reported in respect to control, 4 mg, and 8 mg growth hormone treatment; all finds were insignificant ($p > 0.05$): - healing failure rate (34.6%, 30.8%, 16.7%;) - severe fatty infiltration of > Goutallier grade 3 (34.6%, 23.2%, 20.8%) - functional outcomes/ range of motion/ pain visual analog scale - increased peak IGF-1 levels (186.31 ng/mL, 196.82 ng/mL, 279.43 ng/mL)	No statistically significant improvement in healing or outcomes related to growth hormone treatment

VITAMINS: VITAMIN D

Benefits of vitamin D on bone mineralization and overall health have been well studied as its benefits on soft tissue have grown with literature supporting its importance (Table 4). Ultraviolet radiation from sunlight turns 7-dehydrocholesterol to previtamin D3. In the liver, pre-vitamin D3 is metabolized into 25-hydroxyvitamin D3 (calcifediol). From there, the kidney converts calcifediol to 1,25-dihydroxyvitamin D3. Calcifediol positively influences the accumulation of phosphate into muscle cells, as well as the binding of vitamin D to its receptors on the plasma membranes of myocytes. Once the phosphate moves into the cell, it improves the metabolism of creatine phosphate, helps stimulate growth, and aids in cell proliferation.[31]

Vitamin D has been shown to significantly downregulate the cellular response to TNF-alpha, IL-6, and CRP; when elevated, each of these are known to contribute to inflammation.[32] Oh et al showed that patients with lower Vitamin D levels had higher levels of fatty degeneration in cuff muscles.[33] Recent reports have emphasized that fatty degeneration of the cuff is an irreversible poor prognostic indicator and it would be worthwhile to determine how this progression can be influenced by pharmacologic therapy.[39]

As vitamin D deficiency is common in the general population, it occurs particularly in elderly individuals with secondary muscle weakness often more profound in proximal muscles. Additionally, muscle atrophy of type two muscle fibers has been shown histopathologically and may contribute to the weakness.[34] It is believed that vitamin D deficiency leads to decreased BMP-4 expression via the Notch/BMP signaling pathway, with a resultant decrease in cell growth and proliferation. A randomized controlled study by Sato et al found that low doses of vitamin D increased the relative number and size of type two muscle fibers with improved muscle strength.[35] Interestingly, a course of vitamin D with calcium over a period of three months has been shown to reduce the risk of falling by 49% compared to calcium alone.[36] While the benefits at the cellular level may be beneficial for RCR, vitamin D is imperative for overall musculoskeletal function.

VITAMINES: VITAMIN C

Vitamin C is an antioxidant with the ability to remove reactive oxygen species (ROS) and acts as a cofactor for collagen synthesis (Table 4). Omeroglu et al reported that a local injection of high dose (150mg) vitamin C increases collagen proliferation, diameter of fibers, and number of fibroblasts in a rat study.[40] Hung et al reported that a local injection of Vitamin C in flexor digitorum profundus tendons of chickens resulted in a decrease in tendon adhesions and an increase in glutathione levels due to its antioxidant effect.[37] Morikawa et al evaluated the effect of vitamin C oral supplementation on rotator cuff tendons in superoxide dismutase one deficient mice, reporting improved quantitative histologic measurements.[41] As the superoxide dismutase acts to remove free radicals, they hypothesized that the antioxidant effects of Vitamin C are what led to the improvements.

DePhilipo et al performed a systematic review of Vitamin C supplementation after musculoskeletal injuries.[38] They found that several in vitro studies showed benefit of vitamin C supplementation but clinical studies have been unable to replicate these findings yet. Of note, there were no adverse effects from supplementation reported in any of the clinical studies. Future studies are required to determine if the effects of Vitamin C will translate to clinically relevant results for RCR.

CONCLUSION

RCTs are among the most common injuries of the shoulder, often leading to progressive pain and dysfunction in those affected. This review provides a summary of various potential strategies that can enhance repair in the perioperative and postoperative period. As manipulation of pharmacologic factors shows potential for enhancing healing following RCRs, future studies are needed to establish a viable augmentation strategy to improve patient outcomes.

CONFLICT OF INTEREST

The authors of this paper certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interests pertinent to the subject matter discussed in this manuscript.

AUTHOR CONTRIBUTIONS

Maksim Vaysman, DO

1. Study design, data acquisition, and interpretation
2. Drafting and revising the manuscript
3. Final approval of version to be published
4. Agreement for accountability for all aspects of the work

Matthew G. Alben, BS

1. Study design, data acquisition and interpretation
2. Drafting and revising the manuscript
3. Final approval of version to be published
4. Agreement for accountability for all aspects of the work

Matthew Todd, BS

1. Data acquisition and interpretation
2. Drafting and revising the manuscript
3. Final approval of version to be published
4. Agreement for accountability for all aspects of the work

Charles Ruotolo, MD

1. Study design, oversight, and data interpretation
2. Drafting and revising
3. Final approval of version to be published
4. Agreement for accountability for all aspects of the work

Table 4. Vitamins

Vitamin D					
Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Nossov, 2014[31]	Review of biologic augmentation of tendon-to-bone healing	-	Tendon-to-bone healing in respect to scaffolds, mechanical load, vitamin D, and diabetes	- animal and human cadaver biologic scaffolds for tendon repair yielded equivocal results - rest in the acute inflammatory period is beneficial but mechanical loading and forces are imperative for proper development of the enthesis - supplementation in Vitamin D deficient patients may reduce the incidence or extent of tendon damage as well as tendinopathy - glycemic control reduces morbidity and can minimize complications, such as infection	- scaffold augmentation can improve the initial biomechanical integrity of tendon-to-bone repair with manipulation of biological factors to promote a favorable healing environment
Bahar-Shany, 2010[32]	Analysis of calcitriol modulation of MMP-9 in TNF-alpha treated keratinocytes	- cell culture - gelatin zymography - RT-PCR - western blot analysis - electrophilic mobility shift assay	Pro-MMP-9 secretion	In a dose-dependent manner, calcitriol inhibits pro-MMP-9 secretion by TNF-alpha cells	Effect of calcitriol was significant at 1 nM
Oh et al, 2009[33]	366 consecutive patients with shoulder symptoms underwent magnetic resonance arthrography. There were 228 patients with full thickness tear (Group 1) and 138 patients with other conditions of the shoulder (group 2)	All patients underwent magnetic resonance arthrography and an isokinetic muscle performance test. The serum concentrations of vitamin D were measured.	In general, a lower serum level of vitamin D was related a higher fatty generation in the muscles of the cuff	The serum vitamin D level has a significant negative correlation the fatty degeneration of the cuff muscle and a positive correlation with isokinetic muscle torque.	In group 1, multivariate linear regression analysis revealed that the serum level of vitamin D was an independent variable for fatty degeneration of the supraspinatus and infraspinatus
Ziambaras, 1997[34]	Case Series on 2 patients with significant proximal muscle weakness that gradually resolved over a course of 6 months upon correction of serum 25-hydroxyvitamin D	- one patient had Vitamin D malabsorption treated with daily 50,000 IU PO - one patient had dietary Vitamin D deficiency treated in the hospital with daily 50,000 IU and B12 injections and discharged on 50,000 IUtwice a week with dietary calcium supplementation	Muscle strength	Following correction of Vitamin D levels in the respective patients, muscle strength gradually improved and residual deficits are minimal	- muscle biopsy in one patient revealed type IIB fiber atrophy
Sato, 2017[35]	96 post-stroke hemiplegic women followed for two	Ergocalciferol group received 1,000 IU daily	- number of falls per person	Vitamin D treated group was found to have: - 59% reduction in falls (95% CI, 28-81%; p = 0.003)	- all patients had a deficient

	years: - 48 patients randomly selected to receive daily ergocalciferol - 48 patients randomly selected for the placebo group		- incidence of hip fractures - strength and tissue ATPase of skeletal muscle measured before and after the study	- increase in relative number and size of type II muscle fibers - increased muscle strength - 0 in 48 hip fractures over two-year period, compared to 4 of 48 patients in the placebo group (log-rank, p = 0.049)	25-hydroxyvitamin D at baseline - paper retracted in Cerebrovasc Dis. 2017;44(3-4):240 PMID: 28942438
Bischoff, 2003[36]	122 elderly women in long-stay geriatric care	1200 mg calcium, n=60 1200 mg calcium plus 800 IU cholecalciferol, n=62	Number of falls Change in musculoskeletal function	Before treatment, the mean observed number of falls per person per week was 0.059 in the Cal+D-group and 0.056 in the Cal-group. In the 12-week treatment period, the mean number of falls per person per week was 0.034 in the Cal+D-group and 0.076 in the Cal-group. Musculoskeletal function improved significantly in the Cal+D-group (p = 0.0094)	A single intervention with vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone.

Vitamin C					
Reference	*Participants*	*Exposure*	*Outcome*	*Key Findings*	*Comments*
Hung, 2013[37]	57 female Kamei chickens	FDP injury induced. 50ul of saline, 5mg/ml, or 50mg/ml Vitamin C solution injected	Glutathione(GSH) and oxidized Glutathione(GSSG) levels, Gliding test, Ultrasound imaging, histological examination.	GSH levels decreased at two and six weeks post injury. GSSG increased at six weeks. Both 5 and 5 mg/mL vitamin C had higher levels of GSH at two weeks but no significant change in GSSG. No significant difference in gliding resistance or fibrotic size at two weeks. Improvement in gliding resistance inn vitamin C groups at 6 weeks Histological examination showed less adhesions in vitamin C group	Local injection of vitamin-C solution can reduce the extent of adhesion of healing tendons, probably by redox modulation, in a chicken model
DePhilipo, 2018[38]	Systematic Review	-	-	- 2 studies reported accelerated bone healing - 2 preclinical studies reported increased type 1 collagen and tissue formation in vitamin C groups - 1 study reported significant short-term ACL graft improvements	Level of evidence 2

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