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Original article

Arginine L-alpha-ketoglutarate, methylsulfonylmethane, hydrolyzed type I collagen and bromelain in rotator cuff tear repair: a prospective randomized study

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Abstract

Objective:
Arthroscopic rotator cuff repair generally provides satisfactory result, in terms of decreasing shoulder pain, resulting in improvement in range of motion. Unfortunately, imaging studies have shown that after surgical repair re-rupture rate is potentially high. Literature data indicate that each of the components present in a commercial supplement sold in Italy as Tenosan*(arginine L-alpha-ketoglutarate, methylsulfonylmethane, hydrolyzed type I collagen and bromelain) have a potential role in tendon healing and mitigating the pain due to tendonitis. We evaluated the clinical and MRI results of rotator cuff repair with and without the employment of this oral supplement in patients with a large, postero-superior rotator cuff tear (RCT).

Research design and methods:
We enrolled 90 consecutive patients who had a large, postero-superior RCT. All the lesions were managed with an arthroscopic repair. Patients were randomized and treated either with (Group I) or without (Group II) the supplement. The primary outcomes were the difference between the pre- and post-operative Constant score and repair integrity assessed by MRI according to Sugaya's classification. The secondary outcome was the pre- and post-operative Simple Shoulder Test.

Results:
No statistically significant differences were identified between the two groups for each considered variable, except for shoulder pain (follow-up: 6 months) and repair integrity (final follow-up). Intensity of shoulder pain was lower in the Group I patients ($p < 0.001$). Analogously, in Group I, the percentage of patients with a better repair integrity result was significantly higher than Group II.

Conclusion:
The use of the supplement for 3 months after cuff repair decreases shoulder post-operative pain and leads to a slight improvement in repair integrity. This improvement does not seem to correlate with an better objective functional outcome. However, these effects could facilitate and abbreviate the post-operative rehabilitation program and reduce re-rupture rate. The main limitations of this study are the relative short follow-up period and small number of patients studied.

Introduction

Rotator cuff tear is a common shoulder pathology affecting the adult population that may compromise shoulder function, health status and patient-related

*Tenosan is a registered trade name of Agave farmaceutici, Bologna, Italy.

quality of life[1–3]. Degenerative changes in the cuff tissue are considered the main causes responsible for the tendon tears[4]. When conservative treatment fails to relieve the symptoms of a torn rotator cuff, surgery is considered. Rotator cuff repair typically provides satisfactory results in terms of decreased shoulder pain and improved range of motion[5]. Unfortunately, imaging studies have shown that, with arthroscopic single-row repair, the re-rupture rates vary from 30 to 94%[6,7], with a higher percentage of failure among patients with massive cuff tears. Arthroscopic double-row repair does not appear to lower the re-tear rate. In fact, in three different prospective series, with a mean follow-up of 2 years, the rate of re-tears was 11%, 15% and 17%, respectively[8–10]. Furthermore, it was has been observed that the re-tear rate was higher in patients with larger tears[10]. Recent biomechanical studies demonstrate that although the double-row repair has a high ultimate load to failure, failures usually occur at the muscle–tendon junction or where the medial suture anchors were placed[11,12]. Rotator cuff failure is attributed to age and intrinsic overloading rather than to an extrinsic impingement[13,14].

Information on a possible role of dietary supplements, to be taken following rotator cuff repair, with the aim of reducing post-operative shoulder pain and improving the repair integrity, is still a subject for discussion. Of the possible supplements, L-arginine is commonly used[15]. It has been demonstrated that it is an essential amino acid required by the constitutive enzyme, endothelial NO oxide synthase (eNOS), to produce NO and that the latter is an important paracrine substance released by the endothelium to regulate vasomotor tone. NO is responsible for the vasodilation of the blood vessels. The more NO is released, the greater the increase in vessel diameter, which allows an increased blood flow. Kharitanov[15] and Bode-Böger[16] observed that production of NO is directly related to arginine plasma concentration. One possible explanation of arginine function is that it restores endothelial function in patients with atherosclerosis, in whom there are elevated levels of asymmetric dimethylarginine, an endogenous inhibitor of eNOS[17]. Fitzpatrick *et al.*[18] observed that extracts of grape seeds and skins, grape juice, and many red wines exhibit endothelium-dependent relaxing (EDR) activity *in vitro*. This EDR activity involves endothelial nitric oxide (NO) release and subsequent increase in cyclic GMP levels in the vascular smooth muscle cells.

Murrel *et al.*[19] have demonstrated that inhibition of NO synthase activity with oral administration of N_{ω}-nitro-L-arginine methyl ester (L-NAME) resulted in a significant reduction in cross-sectional area and failure load of the healing Achilles tendon constructs. Rats fed with the same regimen of the enantiomer of L-NAME, (D-NAME) had normal tendon healing. Therefore, the authors concluded that NO synthase is induced during tendon healing and inhibition of NO synthase inhibits this tendon healing. In three randomized clinical trials, it has been shown that NO delivered via a transdermal patch enhances the subjective and objective recovery of patients with different tendinopathies[20–22].

Yuan *et al.*[23] observed that NO-flurbiprofen promoted better collagen reorganization during tendon healing. The enhanced tendon healing by NO-flurbiprofen is likely due to the release of NO from the compound. Finally, Paoloni *et al.*[22] observed that topical glyceryl trinitrate treatment, whose mechanism of action is through the production of NO, significantly improved pain scores, range of motion and muscular force in patients with supraspinatus tendinopathy. Furthermore, the authors added that NO donation may stimulate wound fibroblasts to increase collagen synthesis and remodeling.

Aiyegbusi *et al.*[24] investigated the effects of bromelain on tenocyte proliferation and tendon malondialdehyde (MDA) levels in the early stage of healing in a crush injury of the Achilles tendon in rats and concluded that bromelain given once daily in acute tendon injury promoted healing by stimulating tenocyte proliferation.

These new findings have led the authors to undertake a study to determine whether the oral intake of arginine L-alpha-ketoglutarate, methylsulfonylmethane, hydrolyzed type I collagen and bromelain might mitigate shoulder pain and improve repair integrity of rotator cuff tear of the shoulder after arthroscopic repair. These components are all contained in a commercial supplement sold in Italy as Tenosan. Therefore, we performed a prospective randomized study to assess the clinical and MRI results of single-row arthroscopic rotator cuff repair with and without the employment of this supplement in patients with a large postero-superior rotator cuff tear.

Materials and methods

A power analysis was performed based on the effects of the oral supplement on shoulder pain and integrity repair. Power analysis indicated that a total sample size of 128 patients would provide an 80% power ($\beta = 0.2$, $\alpha = 0.05$), assuming an effect size of 0.5 (mean difference of 5 points and standard deviation of 10 points) to analyze pain using a VAS test. Power analysis indicated that a total sample size of 55 patients would provide an 80% power ($\beta = 0.2$, $\alpha = 0.05$), assuming an effect size of 0.5 (mean difference of 5 points and standard deviation of 10 points) to analyze Constant score and the Simple Shoulder Test. A post hoc power analysis was performed.

We enrolled 90 consecutive patients with a full-thickness large postero-superior rotator cuff tear who met the inclusion criteria. Recruitment started in September 2009 and was completed in April 2011. All patients accepted

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients with large postero-superior repairable full-thickness rotator cuff tear	Age >70 years partial thickness rotator cuff tear
Patients able to complete serial MRI examination	Small or massive full-thickness rotator cuff tear
	Subscapularis tear
	Traumatic rotator cuff tear
	Long head biceps pathologies
	Labral pathologies
	Os acromiale
	GH joint degenerative arthritis
	Autoimmune or rheumatological diseases
	Previous surgery in the same shoulder
	Intolerance to oral integrator

to enter the study and signed a specific informed-consent form according to the Declaration of Helsinki. The ethics committee of our institution approved all procedures described in this study. In all patients the lesion was preoperatively confirmed with a non-arthrographic MRI. Oblique sagittal, oblique coronal, and axial T2-weighted spin-echo MRI scans were obtained (repetition time 3200 milliseconds; echo time 85 milliseconds). We employed T2-weighted, gradient-echo spectral presaturation inversion recovery (SPIR) sequences in true axial scans and T1-weighted, gradient echo SPIR sequences in oblique coronal planes that are parallel to the course of the supraspinatus muscle and oblique sagittal planes that are parallel to the glenoid articular surface. MRI findings represented the main criteria that we used, prior to surgery, for including patients in the study. A radiographic series (true antero-posterior, axillary and outlet views) was used to document radiographic signs of degenerative arthritis. The inclusion and exclusion criteria are summarized in Table 1. Fatty degeneration of rotator cuff muscles was documented on MRI and classified according to Goutallier *et al.*[25] and Fuchs *et al.*[26] (grade 0, no fatty infiltration; grade 1, some fatty streaks; grade 2, more muscle than fat; grade 3, as much muscle as fat; grade 4, less muscle than fat).

We confirmed patients' inclusion at the time of arthroscopy, after verifying the dimension of the cuff tear. We consider as large a full-thickness tear encompassing the entire supraspinatus, with minimal retraction of the tendon ends and measuring 2–4 cm (types CII and CIII according Snyder's classification[27]). These crescent-shaped tears are relatively short and wide. The medial-to-lateral length of these tears is less than the anterior-to-posterior width. The mean time that elapsed from the beginning of the symptoms to the operation was 9 months (from 2 to 16 months).

Pre- and post-operative clinical evaluations, relative to the current study, were performed by two of the authors who had expertise in shoulder surgery but who were not directly involved in the operation. In all cases, evaluations were carried out preoperatively and after 6 (VAS: visual analogue scale: 0 = no distress; 10 = unbearable distress) and 12 months (Constant score[28]; Simple Shoulder Test[29]) postoperatively. Strength measurements were performed using the micro FET2 Force Evaluation and Testing device (Hoggan Health Industries, West Jordan, UT, USA) that measured the maximum strength in pounds after 5 seconds of contraction in the affected arm. Three measurements were taken at 90° of elevation in the scapular plane; successively the three measurements were averaged. MRI studies were performed in all patients preoperatively and 12 months after repair. All scans were evaluated independently by two expert musculoskeletal specialty radiologists who had no knowledge of the patients' clinical details or surgical history. Disagreements were discussed in a consensus meeting, where the scans were re-evaluated and a final decision was taken[30]. Images were acquired for structural and qualitative assessment of the rotator cuff and repair integrity was determined according to Sugaya's classification[10,31]. This distinguishes five repair categories with the use of oblique coronal, oblique sagittal and transverse views of T2-weighted images. Type I indicates a repaired cuff that has sufficient thickness with homogeneously low intensity on each image; type II, sufficient thickness associated with a partial high-intensity area; type III, insufficient thickness without discontinuity; type IV, the presence of a minor discontinuity in more than one slice of each image, suggesting a small tear; type V, the presence of a major discontinuity on each image, suggesting a large tear. All operations were performed by one surgeon (SG), with patients in the beach chair position under general anesthesia and interscalene block. A standard arthroscopic pump was used in all cases and standard posterior, lateral, antero-lateral and mid glenoid portals were used to perform a thorough diagnostic examination. After the intra-articular evaluation, the scope was placed in the subacromial space. Subacromial bursa was removed to gain a clear view of the rotator cuff tear. The footprint area of the greater tuberosity was prepared; successively, using a full radius resector, bleeding of this area was induced. The anchors were placed within the footprint of the rotator cuff. Twinfix Ti 5.0 mm Suture Anchors with #2 preloaded ultrabraid suture were used for this study (Smith & Nephew, Inc., Andover, MA, USA). Each suture was passed through the tendon approximately 15 mm medial to the tear margin. When sutures had been placed, they were sequentially tied in a simple configuration with a sliding SMC knot (Samsung Medical Center)[32] followed by three alternating half-hitches. The number of anchors

used varied from two to three (mean: 2.63). Subacromial decompression was performed in all cases.

Postoperatively, all patients used a sling in internal rotation. Under supervision, passive range of motion was initiated in the first week. The sling was removed 28 days after surgery. Active assisted motion was started after 4 weeks postoperatively and full active range of motion was allowed from 6 to 8 weeks. Strengthening exercises were delayed for 15 weeks. None of the patients took pain medication after surgery.

Randomization lists were generated for treatment assignment; a sealed envelope contained 45 cards on which was printed "WITH–GROUP I" and other 45 cards on which was printed "WITHOUT–GROUP II". Patients were randomized and assigned to one of the two groups of 45 cases each. Randomization was performed 3 days before surgery. Group I consisted of patients who took the oral integrator (two sachets daily for 3 months starting from the first postoperative day); Group II was those who did not take the oral integrator. Surgeon and patients were informed about the randomization the day after the operation.

Ten patients were excluded from the study during the arthroscopic evaluation because they had massive (two tendons involved – type CIV: seven cases) and small (<1 cm – type CI: three cases) rotator cuff tears. Three other patients were excluded because they had diarrhea in the postoperative period (during this time no other drug was administered). The diarrhea ceased after the suspension of the integrator. The cards of these 13 patients were put back into the sealed envelope and another 11 consecutive patients were recruited into the study.

Statistical analysis

The comparison between the two groups for each variable was carried out using Student's *t*-test and the chi-square test for the continuous quantitative and for qualitative variables, respectively. The Mann–Whitney test was used for skewed quantitative data. Fisher's exact test was used for nominal data. The analyzed variables were: age, gender, dominance, fatty degeneration, VAS, Constant score and SST.

A two-tailed analysis of mean (Student's *t*-test) was used to investigate the difference between pre- and post-operative pain factors. Constant score and SST were evaluated with the Mann–Whitney test for non-parametric skewed values.

To evaluate if repair integrity between the two groups was influenced by age, Student's *t*-test was used.

To test the hypothesis that the use of the oral integrator provided superior clinical results in terms of repair integrity, a chi-square test was used.

Cohen's kappa coefficient was used to assess inter-observer agreement with respect to rotator cuff repair integrity on MRI. K-values >0.8 represent almost perfect agreement. For significance level, a *p*-value was set at 0.05. Statistical analysis was carried out using SPSS 19 statistical software.

Results

Although the number of enrolled patients do not correspond to preliminary power analysis, post hoc power analysis suggests that the difference relative to 38 patients does not compromise the validity of our outcomes.

Patient flow through the stages of the study is depicted in Figure 1.

Three patients were lost to follow-up after 1 year; one belonged to Group 1 and two to Group II. Unfortunately we do not know the cause of their lack of follow-up participation. The final evaluation was thus carried out on 87 patients, 42 males and 45 females. The age ranged between 47 and 69 (mean age 62) years. The mean age was 60 for Group I (range: 53–69) years and 62 for Group II (range: 47–69) years.

The mean values relative to pre- and post-operative (6 months) subjective shoulder pain (VAS) in the two groups are summarized in Table 2. Group I patients had, at the intermediate follow-up, a shoulder pain intensity lower with respect to that registered in Group II ($p<0.001$; effect 1.6; 95% CI: 1.29–2.59).

No statistically significant differences were identified between the two groups for each considered variable, except for repair integrity. Results are summarized in Tables 3, 4 and 5.

Decrease in pain level, after 1 year from surgery, between the two groups was not statistically significant ($p=0.312$; effect 2.9; 95% CI: 41.31–46.76) (Table 3).

After 1 year from the surgical repair, MRI showed for the Group I patients, 27 cases (61.4%) with a type I repair, 11 (25.0%) with a type II, four (9.1%) with a type III, two (4.5%) with a type IV, and none with a type V repair. In Group II there were 17 shoulders (39.5%) with a type I repair, ten (23.2%) with a type II, 12 (27.9%) with a type III, three (7.0%) with a type IV and one (2.3%) with a type V (Table 5). The two groups were significantly different in terms of type of repair (type I, II and III), with a *p*-value equal to 0.045 (chi square = 6.218; df = 2). Percentage of re-rupture was 4.5% in Group I and 9.3% in Group II ($p=0.111$). The age of the six patients with re-rupture was: 54, 61, 64, 65, 65, 67 (average = 62.6). The mean age of the remaining patients was 61.2. The final mean Constant score of the six patients with re-rupture was lower (61) than that calculated for the remaining patients of Group I and II. No statistically significant difference in

hypotheses that the NO and/or bromelain have a role during the phase of inflammation which characterizes the initial process of tendon healing[4]. Although the benefit is transient, it permits an assisted and self-managed rehabilitation program to be performed with less apprehension, improving the status of patient satisfaction. Moreover, if the patient has less pain, recovery times are shortened and the cost for rehabilitation is lowered. Although our follow-up was short, we observed only six cases of re-rupture (6.9%) in the two groups. Although number of cases with re-tears is low, failures occurred more frequently in the group thayt did not take the oral supplement ($p = 0.714$). We were surprised to verify such a low incidence of rotator cuff re-tears. However, we believe that this could be attributed to the short follow-up period and to the fact that in our study we did not consider patients with massive tears. Furthermore, our data suggest that cuff re-tears do not seem to be influenced by patient age. The percentage of patients with type I–II repair integrity (according to Sugaya's classification[31]) was 86.4% in the group which took the oral supplement and 62.7% in the group that did not take it ($p < 0.05$). However, this improvement in tissue healing did not correlate with an improved functional outcome. In fact, the two groups had similar pre- and post-operative Constant scores and Simple Shoulder Test. Kluger *et al.*[47] believe that the vast majority of cuff repair failures occurred atraumatically in the first 3 months; however 14% of the re-ruptures might occur 2–5 years postoperatively and can be related to sport activities or direct trauma. Therefore, a higher percentage of type I–II repair integrity, achieved by taking oral supplements, could reduce the number of cases of cuff re-ruptures after a long follow-up period. In conclusion, our study suggests that use of a supplement containing arginine L-alpha-ketoglutarate, methylsulfonylmethane, hydrolyzed type I collagen and bromelain for 3 months after operation decreases shoulder pain during the first 6 post-operative months and leads to a slight improvement in repair integrity of large rotator cuff tears involving the supraspinatus tendon. This improvement does not seem to correlate with a better objective functional outcome. These effects could facilitate and shorten the post-operative rehabilitation program and reduce the percentage of re-ruptures after a long follow-up period. However, many aspects of this study still have to be elucidated and further research is necessary to determine the exact mechanism by which the oral supplement modulates shoulder pain and facilitates the tendon healing.

We are aware that the main limitation of this study is the relative short follow-up period, even though we believe that clinical outcome observed 1 year after surgery should not deteriorate in a medium-term follow-up period. Another limitation is the relative small number of studied patients.

Transparency

Declaration of funding
There are no sponsor to be declared for the study.

Declaration of financial/other relationship
There are no relationships to be declared for any of the authors.

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References

1. McKee MD, Yoo DJ. The effect of surgery for rotator cuff disease on general health status. Results of a prospective trial. J Bone Joint Surg Am 2000;82:970-9
2. Gartsman GM, Brinker MR, Khan M, et al. Self-assessment of general health status in patients with 5 common shoulder conditions. J Shoulder Elbow Surg 1998;7:228-37
3. Hollinshead RM, Mohtadi NG, Vande Guchte RA, et al. Two 6-year follow-up studies of large and massive rotator cuff tears: comparison of outcome measures. J Shoulder Elbow Surg 2000;9:373-81
4. Sharma P, Maffulli N. Biology of tendon injury: healing, modeling and remodeling. J Musculoskelet Neuronal Interact 2006;6:181-90
5. Warner JJ, Tetreault P, Lehtinen J, et al. Arthroscopic versus mini-open rotator cuff repair: a cohort comparison study. Arthroscopy 2005;21:328-32
6. Galatz LM, Ball CM, Teefey SA, et al. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am 2004;86:219-24
7. Boileau P, Brassart N, Watkinson DJ, et al. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? J Bone Joint Surg Am 2005;87:1229-40
8. Lafosse L, Brozska R, Toussaint B, et al. The outcome and structural integrity of arthroscopic rotator cuff repair with use of the double-row suture anchor techniques. J Bone Joint Surg Am 2007;89:1533-41
9. Huijsmans PE, Pritchard MP, Berghs BM, et al. Arthroscopic rotator cuff repair with double-row fixation. J Bone Joint Surg Am 2007;89:1248-57
10. Sugaya H, Maeda K, Matsuky K, et al. Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair. J Bone Joint Surg Am 2007;89:953-60
11. Park MC, Tibone JE, ElAttache NS, et al. Part II: biomechanical assessment for a footprint-restoring transosseous-equivalent rotator cuff repair technique compared with a double-row repair technique. J Shoulder Elbow Surg 2007;16:469-76
12. Smith CD, Alexander S, Hill AM. A biomechanical comparison of single and double-row fixation in arthroscopic rotator cuff repair. J Bone Joint Surg Am 2006;88:2425-31
13. Ozaky J, Fujimoto S, Nakagawa Y, et al. Tears of the rotator cuff of the shoulder associated with pathological changes in the acromion. A study in cadavera. J Bone Joint Surg Am 1988;70:1124-30
14. Ogata S, Uhthoff HK. Acromial enthesopathy and rotator cuff tear. A radiologic and post-mortem investigation of the coracoacromial arch. Clin Orthop 1990;254:39-48
15. Kharitonov SA, Lubec G, Lubec B, et al. L-arginine increases exhaled nitric oxide in normal human subjects. Clin Sci (Lond) 1995;88:135-9
16. Bode-Böger SM, Böger RH, Galland A, et al. L-arginine-induced vasodilation in healthy humans: pharmacokinetic-pharmacodynamic relationship. Br J Clin Pharmacol 1998;46:489-97

17. Gornik HL, Creager MA. Arginine and endothelial and vascular health. J of Nutr 2004; 134(10 Suppl):2880-7s
18. Fitzpatrick DF, Bing B, Maggi DA, et al. Vasodilating procyanidins derived from grape seeds. Ann N Y Acad Sci 2002;957:78-89
19. Murrell GA, Szabo C, Hannafin JA, et al. Modulation of tendon healing by nitric oxide. Inflamm Res 1997;46:19-27
20. Paoloni JA, Appleyard RC, Nelson J, et al. Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. Am J Sports Med 2003;31:915-20
21. Paoloni JA, Appleyard RC, Nelson J, et al. Topical glyceryl trinitrate treatment of chronic noninsertional achilles tendinopathy. A randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am 2004;86-A:916-22
22. Paoloni JA, Appleyard RC, Nelson J, Murrell GA. Topical glyceryl trinitrate application in the treatment of chronic supraspinatus tendinopathy: a randomized, double-blinded, placebo-controlled clinical trial. Am J Sports Med 2005;33:806-13
23. Yuan J, Murrell GA, Wei AQ, et al. Addition of nitric oxide via nitroflurbiprofen enhances the material properties of early healing of young rat Achilles tendons. Inflamm Res 2003;52:230-7
24. Aiyegbusi AI, Duru FI, Anunobi CC, et al. Bromelain in the early phase of healing in acute crush Achilles tendon injury. Phytother Res 2011;25:49-52
25. Goutallier D, Postel JM, Bernageau J, et al. Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin Orthop 1994;304:78-83
26. Fuchs B, Weishaupt D, Zanetti M, et al. Fatty degeneration of the muscles of the rotator cuff: assessment by computed tomography versus magnetic resonance imaging. J Shoulder Elbow Surg 1999;8:599-605
27. Snyder SJ. Arthroscopic classification of rotator cuff lesions and surgical decision making. In Shoulder Arthroscopy, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2003:201-7
28. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop 1987;214:160-4
29. Lippit SB, Harreyman DT, Matsen FA. A practical tool for evaluating shoulder function. The Simple Shoulder Test. In: Matsen FA, Fu FH, Hawkins RJ, eds. The Shoulder: a Balance of Mobility and Stability. Rosemont, IL: American Academy of Orthopedic Surgeons, 1993:501-18
30. Burks RT, Crim J, Brown N, et al. A prospective randomized clinical trial comparing arthroscopic single and double row rotator cuff repair: magnetic resonance imaging and early clinical evaluation. Am J Sports Med 2009;37:674-82
31. Sugaya H, Maeda K, Matsuki K, et al. Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation. Arthroscopy 2005;21:1307-16
32. Kim SH, Yoo JC. Arthroscopic knot tying. Tech Shoulder Elbow Surg 2003;4:35-43
33. Barber FA, Coons DA, Ruiz-Suarez M. Cyclic load testing of biodegradable suture anchors containing 2 high-strength sutures. Arthroscopy 2007;23:355-60
34. Bardana DD, Burks RT, West JR, et al. The effect of suture anchor designed and orientation on suture abrasion: an in vitro study. Arthroscopy 2003;19:274-81
35. Cummins CA, Murrel GA. Mode of failure for rotator cuff repair with suture anchors identified at revision surgery. J Shoulder Elbow Surg 2003;12:128-33
36. Mahar A, Allred DW, Wedemeyer M, et al. A biomechanical and radiographic analysis of standard and intracortical suture anchors for arthroscopic rotator cuff repair. Arthroscopy 2006;22:130-5
37. Liem D, Lichtenberg S, Magosh P, et al. Magnetic resonance imaging of arthroscopic supraspinatus tendon repair. J Bone Joint Surg Am 2007;89:1770-6
38. Fung HL. Clinical pharmacology of organic nitrates. Am J Cardiol 1993;72:9-13
39. Berrazueta JR, Losada A, Poveda J, et al. Successful treatment of shoulder pain syndrome due to supraspinatus tendinitis with transdermal nitroglycerin: a double blind study. Pain 1996;66:63-7
40. Arnoczky SP, Tian T, Lavagnino M, et al. Activation of stress-activated protein kinases (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. J Orthop Res 2002;20:947-52
41. Yuan J, Murrell GA, Wei AQ, et al. Apoptosis in rotator cuff tendonopathy. J Orthop Res 2002;20:1372-9
42. Freedman JE, Parker 3rd C, Li L, et al. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation 2001;103:2792-8
43. Tassman G, Zafran J, Zayon G. A double-blind crossover study of a plant proteolytic enzyme in oral surgery. J Dent Med 1965;20:51-4
44. Kelly GS. Bromelain: a literature reviewed and discussion of its therapeutic applications. Altern Med Rev 1996;1:243-57
45. Klein MB, Yalamanchi N, Pham H, et al. Flexor tendon healing in vitro: effects of TGF-beta on tendon cell collagen production. J Hand Surg Am 2002;27:615-20
46. Shakibaei M, Buhrmann C, Mobasheri A. Anti-inflammatory and anti-catabolic effects of TENDOACTIVE® on human tenocytes in vitro. Histol Histopathol 2011;26:1173-85
47. Kluger R, Bock P, Mittlböck M, et al. Long-term survivorship of rotator cuff repairs using ultrasound and magnetic resonance imaging analysis. Am J Sports Med 2011;39:2071-81