

# The risks of local aprotinin injections for treating chronic tendinopathy

John Orchard, Jamie Hofman and Richard Brown

Overuse or degenerative tendon injuries (tendinopathies) are common in sport, certain occupations and even everyday life. They are difficult to treat because of the high failure rate of treatment, tendency towards chronicity and risk of recurrence.

Cortisone injections have been used as a standard management option for tendinopathy for many years and in fact remain the only 'indicated' form of injectable treatment in most countries. There is some evidence that cortisone injections are successful at treating shoulder tendinopathy<sup>35</sup> and tennis elbow<sup>31,33</sup> in the short-term but very little evidence that cortisone injections are useful for patellar tendinopathy<sup>12</sup> or Achilles tendinopathy<sup>26</sup>. Cortisone injections appear to be effective at giving pain relief from tendinopathy in the short-term, which may be due to inhibition of prostaglandins<sup>21</sup>. It is also known that cortisone injections weaken tendons and are possibly associated with tendon rupture. Therefore they are often considered contraindicated for heavy load-bearing tendons such as Achilles tendons in athletes<sup>32,33</sup>.

The scientific evidence base for managing overuse tendinopathies is limited. Some conservative treatment options, such as eccentric exercise<sup>3,30</sup> and nitrate patches<sup>28,29</sup>, show promise in treating various tendinopathies. Alternate injections to cortisone have been described, such as aprotinin, calcium gluconate, auto-injection of patient's own blood, dextrose, dry needling and saline with local anesthetic<sup>27</sup>. This form of treatment is sometimes referred to as prolotherapy (meaning a treatment that causes tissue proliferation).

Aprotinin is a drug which is particularly good at preventing blood loss during major surgery, its major indication<sup>7</sup>. Aprotinin is a broad

spectrum serine protease inhibitor, with particular inhibition of trypsin, plasmin and kallikrein<sup>14</sup>. It is a strongly basic polypeptide, which is currently derived from bovine lungs, with a half life of approximately seven hours<sup>14</sup>. It may block matrix metalloproteinases (MMPs), including MMP-1, MMP-8 and MMP-13 (collagenases) and MMP-2 and MMP-9 (gelatinases), either directly<sup>11</sup> or via inhibition of plasminogen and plasmin<sup>23</sup>. It has been used in injection form for management of chronic tendinopathy in Italy<sup>9</sup>, France<sup>5</sup>, England<sup>25</sup> and Australia<sup>27</sup>.

There has been one randomised double-blind controlled trial published showing statistically-significant superior results to both cortisone injection and placebo injection in patellar tendinopathy at 12 month follow up<sup>9</sup>. For treatment of Achilles tendinopathy, there has been one semi-controlled study showing promising results with aprotinin injections<sup>8</sup> and one recent other substantive case series, with good clinical results, published<sup>5</sup>. Aprotinin has been used (with clinical success) to treat tendinopathies in France since the 1970s<sup>17,18</sup>.

Aside from the limited published trials showing a moderate level of evidence of efficacy, the use of aprotinin is particularly attractive when compared to cortisone (the 'standard' injectable treatment) in chronic tendinopathy as it (aprotinin) probably affects tendon as a collagenase inhibitor. Aprotinin has been used successfully as an agent to promote tendon healing

after surgery (as a component of 'fibrin glue')<sup>22</sup>. Unlike cortisone, aprotinin is a pro-fibrotic agent and is theoretically likely to lead to tendon proliferation rather than degeneration, although this has not been proven to date. Collagenases (MMP-1 and MMP-13) and gelatinases (MMP-2 and MMP-9) have been shown to be present in excessive proportions in patellar tendinopathy<sup>16</sup>, Achilles tendinopathy<sup>1,20</sup> and rotator cuff tendinopathy<sup>24</sup>, although MMP-3 (a stromelysin) has been shown to have decreased concentrations in Achilles tendinopathy<sup>1,20</sup> and rotator cuff tendinopathy<sup>24</sup>. Aprotinin has been shown to inhibit osteoblast-mediated degradation of type-I collagen in vitro<sup>34</sup>. Aprotinin may also possibly have an effect on the neovascularisation in tendinopathy, which is an area of recent focus for treatment of tendinopathy<sup>2</sup>.

The major potential negative of using aprotinin is the side effect of allergy, which is well described in the anaesthetic literature<sup>6,13</sup>. The rate of allergic reaction with initial exposure is very low, but approaches 3% when re-exposure occurs within 3-6 months<sup>6,13</sup>. The controlled trials of aprotinin use for tendon injuries described very few problems with allergy (two patients out of 32 had a 'local' allergic reaction in one study)<sup>9</sup>, although a rate of 11% of patients suffering allergic reactions was reported by Aubin et al<sup>5</sup>. This paper did not give detail regarding the severity of the allergies. Eleven deaths have been reported due to allergic reaction associated with intravenous use of

aprotinin<sup>6</sup>, although in these cases the patients were also compromised with a pre-existing cardiac complaint. From a safety viewpoint, it is also worth noting that doses used in major surgery are approximately 20 times greater than for tendon injections and are injected intravenously rather than subcutaneously. The test (loading) dose in major surgical cases is close to the therapeutic dose for tendon injections.

The primary author of this paper (JO) has been using aprotinin for peritendinous injection of chronic tendinopathies since the year 2000. No major side effects were observed in the first two years of use of this drug, over which the number of injections would have been in the hundreds. The clinical success of this drug led to an increasing number of referrals being made to the practice of the primary author and frequency of treatments. During 2003-2004, when a greater number of injections were being used, a significant number of allergic reactions were noted, prompting this case series review.

The objective of this study was a chart review and clinical follow-up of all patients who had been treated for a tendon injury with the aprotinin brand Trasylol (Bayer, Leverkusen, Germany) over the period February 2003-June 2004 by the primary author at either of two clinics, particularly to assess the rate of adverse reactions.

## Methods

A chart review of all patients for which aprotinin was used for tendon injections over the designated time period was performed by the second author (JH). The name and address of the patient was noted, along with diagnosis, time of symptoms, level of sport, dosage used and follow up recorded in the medical records.

A standard questionnaire was developed to assess side effects and perceived clinical response to aprotinin (see attached Appendix 1). The questionnaire was sent to the last known address of the patient, along with a return stamped envelope. If no response was received within a month, a further questionnaire was sent. If no response was received within two weeks of this second mailout, the second author (JH)

attempted to contact the patient by phone to ask the same questions.

The response to the mailout for the general population was good, although, for professional athletes (who made up a significant proportion of the patient population), the response was quite poor. This is understandable as they receive large amounts of mail compared to the general population. With respect to the professional athletes, some information was able to be obtained by conference with the athlete's team doctor or referring (treating) doctor. In 10 cases, this information was of sufficient quality that the data was included in the analysis. These additional inclusions were important, as two of these cases included significant potential side effects.

## Results

There were 121 patients treated with aprotinin over the designated time period, for 155 different tendinopathy conditions (cases). Thirty-seven cases involved females and 118 involved males. Sixty cases involved athletes playing or competing at professional or elite level, with the most common sports being track and field, Rugby Union and Rugby League. The average age of patients was 35.1 years. The average duration of symptoms was 15 months.

A total of 422 aprotinin injections were used, an average of 2.7 per patient. The most common conditions injected were: Achilles mid-substance tendinopathy (151 injections), Achilles insertional tendinopathy (48 injections), patellar tendinopathy (98 injections), medial hamstring insertional tendinopathy (31 injections), proximal hamstring origin tendinopathy (29 injections) and lateral epicondylitis (27 injections).

The standard protocol of injection was 3 ml of aprotinin mixed with 2 ml of 2% lignocaine plain. The aprotinin was drawn up with a fresh needle from a vial of 50ml Trasylol containing 500,000 KIU, which was stored in a cool cupboard or refrigerator. Trasylol is only available in Australia in 50 ml or 100 ml vials (and is similarly only available in large vials in the USA). The 3 ml dose of active agent used was 30 000 KIU. This is a slightly lower dose

than that used by Capasso et al<sup>9</sup>, with the strength of aprotinin diluted by local anaesthetic. Because local anaesthetic is acidic and aprotinin is basic, this mixture appeared to be associated with minimal pain during the injection process.

The patients were instructed that the injections should not interfere with the mainstay of treatment for tendinopathy, which is eccentric exercises and moderate tendon loading<sup>27</sup>. Apart from resting for the remainder of the day after the injection, the patients were not only permitted to load the tendon moderately the day after the injection, they were also actually encouraged to, by continuing their eccentric exercises and exercising as they were previously (within pain limits).

Generally patients were advised to wait a minimum of one to two weeks between each injection, as per the protocol of Capasso et al<sup>9</sup>. However, this varied and with some patients there were many months between injections.

Of the 155 conditions treated, adequate follow up was achieved regarding 124 of them, a response rate of 80%. The other cases were all non-responders, with no patient making contact but refusing to divulge follow-up details. The average duration between initial injection and follow-up was 9.3 months (SD 6.3 months). Only eight cases were followed up at less than three months. Follow-up was achieved for all known cases of allergic reaction or tendon rupture, including two cases which did not respond by questionnaire initially (as mentioned in the methods). There were seven further cases in professional or elite athletes where adequate follow-up was not achieved (and hence these were not included in the series) but where it was observed that all had returned to full competition (eg, Olympic Games, professional football competitions).

Side effects of injections (perceived or actual) were quite common (Table 1), although the majority were not severe. In 78 cases there were no side effects, with 46 cases having associated side effects (possibly related to the injection). Thirty percent of patients reported having

itch at the injection site, making this the most common side effect. This is thought therefore to represent a common side effect of local aprotinin injection, despite the facts that patients were warned prior to injection about this risk and itch is a symptom which may be exaggerated by the power of suggestion.

There were no side effects of infection from the cases followed up. However, there were 19 cases (10%) with side effects that may have represented allergic reactions (severe itch, nausea, sweating or rash). In seven of these cases (6%), a definite systemic allergic reaction was considered to have occurred, based

**Table 1 – Frequency of associated side effects**

SIDE EFFECT	NUMBER	% (PER CASE)*
Itch, slight	27	22
Itch, severe	10	8
Rash	12	10
Sweating	9	7
Post-injection pain	9	7
Nausea/abdominal cramps	8	6
Systemic allergic reaction	7	6
Headache	5	4
Tendon damage	2	2
Post-injection bleeding	1	1

\* As the average case had 2.7 injections used, the per injection rate is lower than this. Patients were only asked which side effects they had suffered, not on how many occasions they had suffered each. However, the systemic allergic reactions were only suffered once as no patient had a repeat injection after this time.

on the presence of multiple significant systemic symptoms. Four patients were treated within 30 minutes of the aprotinin injection with subcutaneous adrenaline (epinephrine), which resulted in successful reversal of the allergic symptoms. No patient had a drop in blood pressure or required hospitalisation or further management other than a single epinephrine injection. However, the patients treated with epinephrine may have deteriorated further if anti-allergy treatment was not given.

Of concern is that two patients described symptoms that were

considered to be due to systemic allergic reactions (sweating, nausea, abdominal pain within one hour of the injection) but had left the clinic and therefore were not medically observed with these symptoms.

No serious allergic symptoms occurred on the first injection for any patient in the study. This makes the observed rate of systemic allergic reaction 0% on the first injection and 2.6% on subsequent injections.

The interval between last and second last injections for the cases of systemic allergic reaction was 7, 7, 8, 14, 21, 21 and 40 days respectively, with an average of 17 days. Three systemic allergic reactions occurred on the patient's second exposure to aprotinin, two on the third and two on the fourth exposure. The average interval between injections for cases where no allergic reaction occurred was 31 days.

There were two cases of tendon rupture which both occurred to the Achilles tendon. One case of partial rupture occurred many months after the use of aprotinin in an elite hurdler, who had subsequently sought treatment elsewhere with a cortisone injection for a recurrence of the condition. This patient felt that the cortisone injection may have possibly been related to the tendon rupture but that it was unlikely that the aprotinin injections were related, because of the time delay and more recent use of cortisone. This occurrence of partial tendon rupture is therefore considered unlikely to have been a complication of aprotinin use in this case.

The second case involved a high level Rugby League player, who had a course of three aprotinin injections over three weeks for long-standing Achilles tendinopathy, and suffered a complete rupture of the Achilles tendon in a game five days after the third injection. He also had a past history of panhypopituitism which was being treated at the time with anabolic steroid supplementation.

He felt that the aprotinin injections had improved his Achilles tendon pain and allowed him to continue playing, when the severity of the tendon pain meant that "he should have been resting from playing", and therefore he did not attribute the rupture to the aprotinin injections. He underwent

a successful Achilles tendon repair and returned to play in the following season. In this subsequent season he suffered contralateral Achilles tendinopathy and returned for further aprotinin injections (not included in this series, but incidentally with a successful result), but this time waited three weeks after the final injection to return to play. The occurrence of tendon rupture in this case is considered moderately likely to have been associated with the use of aprotinin, with the possible mechanism that pain relief achieved from the injection may have allowed the athlete to continue high risk activities for tendon rupture. Direct chemical damage to the tendon from aprotinin can not be entirely ruled out, but is considered improbable.

In general, there was good progress of the patients' conditions, with 69% of patients improved, 29% similar and 2% worse at the time of follow up. Of the conditions that had improved, the majority were substantially improved (46% of the total number of conditions treated) – see Table 2

The patients' impression of the value of injection was also reasonably impressive. No patients thought that the injection made the condition worse, although 38% were unsure that the injection(s) affected them either way. The remaining 62% were almost evenly split between thinking that the injection(s) may have helped them or definitely helped them. Both patients who suffered the tendon ruptures did not attribute this to the use of aprotinin.

## Discussion

This study confirms clinical results that are compatible with those described

**Table 2 – Patient assessment of progress of condition at the time of follow-up (average 9 months)**

PROGRESS STATUS	NUMBER	%
Completely cured	10	8
No pain but reduced exercise	10	8
Much better	37	30
Slightly better	29	23
Similar	36	29
Slightly worse	1	1
Much worse	1	1

in previous published controlled trials<sup>8,9</sup>, but shows a risk of systemic allergic reaction (6% of cases, or 2.6% per injection subsequent to the first) that was not described in these trials. An even higher rate of allergic reaction (11% or seven out of 62 patients) was described in a previous case series, in which patients were given an average of four injections of aprotinin at an average interval of seven days<sup>5</sup>. However, in this case series the details of allergic reaction (and whether local or systemic) were not presented.

**Table 3 - Impression of injection**

IMPRESSION	NUMBER	%
I am sure that the treatment completely cured my condition	7	6
I am sure that the treatment made my condition better	31	25
I think that the treatment may have made my condition better	39	31
I am unsure whether the treatment did anything	47	38
I think that the treatment may have made my condition worse	0	0
I am sure that the treatment made my condition worse	0	0

If local aprotinin injections are used in rapid succession (ie, within 1-3 months), the risk of systemic allergic reaction on subsequent injections appears to be similar to the 2.8% risk

described in the anaesthetic literature<sup>6</sup>. Fortunately the degree of anaphylactic reaction is probably always going to be less from a local injection with 30,000 KIU than an intravenous dose of 10-20 times this amount. Methods which have been described in the literature to guard against anaphylactic reaction have been to limit the use of the drug when there has been recent exposure, to take prophylactic anti-histamine medication and to check for sensitivity with skin prick tests and to take serum samples for aprotinin-specific IgG. The risk of anaphylactic reaction is reported to drop substantially after three months has passed since prior exposure and is almost non-existent if aprotinin-specific IgG is not detectable in serum<sup>6,13</sup>.

The risk of allergic reaction is therefore substantial with repeated exposure and patients must be alerted of this prior to their being offered repeat aprotinin treatment. Any patient who has a history of allergy to animal products or other major anaphylactic reaction from any cause should probably not be offered aprotinin. In addition, all patients should wait at the medical centre for 30-60 minutes after the injection, so that any signs of allergy can be treated. Two of the patients early in this series had left the practice soon after their injection and did not return but called up later to describe symptoms which probably constituted an allergic reaction, and which came on within an hour.

Because of the risk of anaphylactic reaction, which could be severe and even potentially life-threatening, aprotinin should not be chosen as first line therapy for tendinopathy ahead of safer treatments like eccentric exercise and topical nitrates. However, for load-bearing tendons it could be chosen ahead of cortisone because of an increasing likelihood of tendon healing, and could be chosen ahead of surgery as the combined risks of major complications with surgery (eg, infection, DVT, tissue damage) are probably of greater concern in many cases than the risk of allergy.

The clinical success of injections and minimal number of cases where the tendinopathy condition was worsened in this series gives further encouragement to additional

trials on aprotinin as a treatment for tendinopathy. However, the recommended protocol to be assessed probably should not include repeat injections within two months. Basic science evidence is supportive of the use of aprotinin for tendinopathy of an overuse nature, particularly compared to cortisone injections. This work suggests that aprotinin may assist tendon healing (by reversing the effects of collagenases which break down tendon) whereas cortisone will tend to weaken tendons.

Although aprotinin can reverse the effects of drugs such as heparin and streptokinase, it appears to have no negative pro-thrombotic effects. When used in cardiothoracic surgery, aprotinin is associated with reductions in perioperative stroke with no increase in deep venous thrombosis or graft thrombosis<sup>7</sup>.

In Australia, aprotinin is only available in 50 ml or 100 ml vials, which are not recommended for multi-dose use due to potential risk of contamination<sup>15</sup>. Either these should be used as a single-use therapy or great care must be taken to avoid contamination.

A further proposed complication of aprotinin treatment is the potential to contract bovine spongiform encephalopathy (BSE)<sup>10</sup>. Since this potential complication was raised, Bayer, which is the major manufacturer of aprotinin, has outlined the precautions taken to make sure that aprotinin does not contain viral prions<sup>19</sup>. Steps taken include that the product is only sourced from countries with no BSE, that the tissue used is in the lung (rather than neural tissue) and that a purification process is undertaken. There have been no suspected cases of BSE transmission in 40 years of aprotinin use.

A consent form has been developed as a result of the complications seen in this study to warn patients of the risk of aprotinin therapy, particularly to counsel regarding risks of allergic reaction. The only proposed risks not mentioned on the consent form are those which are thought to be either effectively zero or not related to aprotinin therapy (risks of BSE and thrombotic complications).

There have been recent attempts to manufacture aprotinin-like polypeptides in a recombinant fashion that could potentially give similar clinical effects yet not lead to nearly the same degree of allergic reactions<sup>4</sup>. If this is successfully introduced to the market (and hence allergy becomes a far less likely complication), aprotinin may become a first-line treatment for tendinopathy.

Aprotinin is a promising treatment for tendinopathy, with moderate current evidence to support its use in the form of controlled studies. This study shows results which are compatible with the previous work but illustrates the high risk of allergy with repeated aprotinin injections. There is a need for informed consent, screening of suitable patients and preparation of an emergency plan for an allergic reaction.

**John Orchard and Richard Brown are at The University of New South Wales and Jamie Hofman at the Free University of Amsterdam.**

**Survey and Consent forms can be obtained from [info@injuryupdate.com.au](mailto:info@injuryupdate.com.au)**

**References**

1. Alfredson H, Lorentzon R, Backman S et al. cDNA-arrays and real time quantitative PCR techniques in the investigation of chronic human Achilles tendinopathy. *J Orthop Res* 2003;21:970-5.
2. Alfredson H, Ohberg L. Neovascularisation in chronic painful patellar tendinosis—promising results after sclerosing neovessels outside the tendon challenge the need for surgery. *Knee Surg Sports Traumatol Arthrosc* 2005;13:74-80.
3. Alfredson H, Pietila T, Jonsson P et al. Heavy-Load eccentric calf-muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med* 1998;26:360-6.
4. Apeler H, Peters J, Schroder W et al. Expression, purification, biochemical and pharmacological characterization of a recombinant aprotinin variant. *Arzneimittelforschung* 2004;54:483-97.
5. Aubin F, Javaudin L, Rochcongar P. Case report of aprotinin in Achilles tendinopathies with athletes (French). *Journal de Pharmacie Clinique* 1997;16:270-73.
6. Beierlein W, Scheule A, Dietrich W et al. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Annals of Thoracic Surgery* 2005;79:741-8.
7. Bojanov G, Belani K. Aprotinin - an update for the perioperative physician. *Annals of Cardiothoracic anaesthesia* 2005;8:75-80.
8. Capasso G, Maffulli N, Testa V et al. Preliminary results with peritendinous potase inhibitor injections in the management of Achilles tendinitis. *J Sports Traumatol Rel Res* 1993;15:37-40.
9. Capasso G, Testa V, Maffulli N et al. Aprotinin, corticosteroids and normosaline in the management of patellar tendinopathy in athletes: a prospective randomized study. *Sports Exercise and Injury* 1997;3:111-5.

**Table 4 – Potential side effects associated with aprotinin injections.**

SIDE EFFECT	ESTIMATED RISK
Minor allergic reaction (e.g. itch)	Very common (up to 30%).
Systemic allergic reaction	Rare with initial injection (1 in 1000 reported in anesthetics). Not uncommon thereafter (up to 3% per injection). Spacing injections out (> 6weeks between treatments) reduces this risk, as may anti-histamine treatment and use of skin prick tests.
Worsening of patient's condition	Appears to be uncommon. Physical damage from tendon injection is unlikely if no attempt is made to penetrate the tendon with the injection technique. As a collagenase inhibitor, it is unlikely that there will be any chemical damage to the tendon.
Tendon rupture	There is a risk of tendon rupture with continued loading. Aprotinin has a short half-life and theoretically should not cause tendon weakening. It is unlikely that aprotinin contributes to the risk of tendon rupture, other than by assisting the return to risk activity.
Other cardiovascular condition	In surgery, aprotinin reduces bleeding but does not appear to increase the risk of thrombosis. Therefore this complication is probably no more common than baseline risk.
Contamination from use of multi-dose vial	This risk is very low but potentially present if needles are ever reused. Obviously needles should be single-use and ideally vials should be single-use as well
BSE	This risk is so low as to not be calculable and is not included in the Bayer product information warnings as of 2004.

10. Cederholm-Williams S. Fibrin glue [letter]. *BMJ* 1994;308:1570.
11. Chu S, Yang S, Lue K et al. Regulation of gelatinases expression by cytokines, endotoxin, and pharmacological agents in the human osteoarthritic knee. *Connective Tissue Research* 2005;45:142-50.
12. Cook J, Khan K. What is the most appropriate treatment for patellar tendinopathy? In MacAuley D, Best T eds. *Evidence-based Sports Medicine*. London: BMJ Books, 2002:422-42.
13. Dietrich W, Spath P, Zuhlsdorf M et al. Anaphylactic reactions to aprotinin reexposure in cardiac surgery. *Anesthesiology* 2001;95:64-71.
14. Dollery C. *Therapeutic druged*. Edinburgh: Churchill Livingstone, 1991.
15. Druce J, Locarnini S, Birch C. Isolation of HIV-1 from experimentally contaminated multidose local anaesthetic vials. *Med J Aust* 1995;162:513-5.
16. Fu S, Chan B, Wang W et al. Increased expression of matrix metalloproteinase 1 (MMP1) in 11 patients with patellar tendinosis. *Acta Orthop Scand* 2002;73:658-62.
17. Genety J, Pernin E. Utilisation du Zymofren dans le traitement des tendinites chez le sportif. *Cahiers Med Lyon* 1971;47:135-9.
18. Geudj E. La tendinite achilleenne chez jeune sportif. [MD thesis]. Lyon, 1973.
19. Golker C, Whiteman M, Gugel K et al. Reduction of the infectivity of scrapie agent as a model for BSE in the manufacturing process of Trasylol®. *Biologicals* 1996;24:103-11.
20. Ireland D, Harrall R, Curry V et al. Multiple changes in gene expression in chronic human Achilles tendinopathy. *Matrix Biology* 2001;20:159-69.
21. Khan M, Li Z, Wang J. Repeated exposure of tendon to prostaglandin-E2 leads to localized tendon degeneration. *Clin J Sport Med* 2005;15:27-33.
22. Komurcu M, Akkus O, Basbozkurt M et al. Reduction of restrictive adhesions by local aprotinin application and primary sheath repair in surgically traumatized flexor tendons of the rabbit. *J Hand Surg [Am]* 1997;22:826-32.
23. Lee E, Vaughan D, Parikh S et al. Regulation of matrix metalloproteinases and plasminogen activator inhibitor-1 synthesis by plasminogen in cultured human vascular smooth muscle cells. *Circulation Research* 1996;78:44-9.
24. Lo I, Marchuk L, Hollinshead R et al. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. *American Journal of Sports Medicine* 2004;32:1223-9.
25. Maffulli N, Testa V, Capasso G et al. Calcific insertional Achilles tendinopathy. Reattachment with bone anchors. *American Journal of Sports Medicine* 2004;32:174-82.
26. McLauchlan G, Handoll H. Interventions for treating acute and chronic Achilles tendinitis. *The Cochrane Database of Systematic Reviews* 2001:CD000232.
27. Orchard J. Tendon injections: does it matter what you use? *Sport Health* 2003;21 (3):25-7.
28. Paoloni J, Appleyard R, 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;86A:916-22.
29. Paoloni J, Appleyard R, 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.
30. Roos E, Engstrom M, Lagerquist A et al. Clinical improvement after 6 weeks of eccentric exercise in patients with mid-portion Achilles tendinopathy -- a randomized trial with 1-year follow-up. *Scand J Med Sci Sports* 2004;14:286-95.
31. Santini A, Frostick S. How should you treat tennis elbow? In MacAuley D, Best T eds. *Evidence-based Sports Medicine*. London: BMJ Books, 2002:351-67.
32. Shrier I, Matheson G, Kohl H. Achilles tendonitis: are corticosteroid injections useful or harmful? *Clin J Sport Med* 1996;6:218-9.
33. Speed C. Corticosteroid injections in tendon lesions. *British Medical Journal* 2001;323:382-6.
34. Tumber A, Papaioannou S, Breckon J et al. The effects of serine proteinase inhibitors on bone resorption in vitro. *Journal of Endocrinology* 2003;178:437-47.
35. van der Windt D, Koes B. Are corticosteroid injections as effective as physiotherapy for the treatment of a painful shoulder? In MacAuley D, Best T eds. *Evidence-based Sports Medicine*. London: BMJ Books, 2002:289-317.