Acta Orthop. Belg., 2020, **86 e-SUPPLEMENT** 3, 88-93

ORIGINAL STUDY

Prolotherapy as a treatment choice for lateral ankle ligament injuries in elite athletes : a case series

Dror MAOR, Mary H. JONES, Justin C. LEE, Andrew J. DUNN, Andy M. WILLIAMS, James D.F. CALDER

From the Fortius Clinic, London, United Kingdom

Injuries to the lateral ankle ligaments are among the most common sustained in professional football. The return to elite level sport within a predictable timeframe after injury is a key aim of the medical team managing professional athletes. Prolotherapy involves injection of dextrose/sucrose injection into injured tissues which is presumed to stimulate the body's self-healing mechanisms, leading to the re-establishment of structural integrity and improved function. This study reports on the results of prolotherapy used to treat anterior talofibular ligament (ATFL) and anterior inferior tibiofibular ligament (AITFL) injuries in elite level athletes and describes the time to return to play (RTP) and rate of reinjury. Patients who had undergone prolotherapy treatment since February 2014 under the care of three specialist sports musculoskeletal radiologists for ankle sprains were identified using the patient database. A retrospective review of the patients medical and rehabilitation records was then carried out. A literature review was carried out to identify the RTP times for conservative and surgical treatments of ATFL and AITFL injuries to allow comparisons with prolotherapy treatments to be made. Standard rehabilitation protocols were then followed and managed by the clubs. Nine elite athletes where treated with prolotherapy for isolated lateral ankle ligament tears since February 2014. Mean age was 23.7 years. Grade III ATFL RTP mean duration was 62 days and AITFL Grade IIa RTP was also 62 days. Importantly there were no reinjuries in any of the prolotherapy groups. To our knowledge this is the first study investigating prolotherapy treatment of ATFL/AITFL in elite athletes. Prolotherapy is safe and appears effective as no re-injuries were identified. However our results have not demonstrated any improvement in RTP when compared to similar injuries treated conservatively without prolotherapy.
Level of Evidence : IV

Keywords : Prolotherapy ; ankle sprain ; lateral ligament injury ; athlete.

INTRODUCTION

The return to elite level sport within a predictable timeframe after injury is a key aim of the medical team managing professional athletes. Ideally this is performed in the shortest time possible, without compromising tissue-level healing and avoiding re-injury *(4,33)*.

■ Dror Maor[1,2],
■ Mary H. Jones[1],
■ Justin C. Lee[1],
■ Andrew J. Dunn[1],
■ Andy M. Williams[1],
■ James D.F. Calder[1,3]
[1]*Fortius Clinic, London, United Kingdom*
[2]*Department of Orthopaedic Surgery, Sourasky Medical Centre, Tel Aviv, Israel*
[3] *Department of Bioengineering, Imperial College, London, United Kingdom*
Correspondence : Dror Maor, *Fortius Clinic, London, UK.*
E-mail : Dror.Maor@fortiusclinic.com

No benefits or funds were received in support of this study.
The authors report no conflict of interests.

Ankle injuries account for 10-18% of all injuries in professional football players. *(7,11,13,14,18,36)*. Injuries to the anterior talofibular ligament (ATFL) or anterior inferior tibiofibular ligament (AITFL) are among the most common sustained in professional football *(2,7)*. Ligament sprains have been shown to account for over 67% of all ankle injuries, of which over 80% were to the lateral ligament complex *(32)*. Therefore, a professional football team is likely to suffer four or five ankle sprains each season *(32)*.

Prolotherapy involves injection of dextrose/ sucrose injection into injured tissues. Perhaps controversially it has also been referred to as regenerative injection therapy (RIT), and is presumed to stimulate the body's' self-healing mechanisms, leading to the re-establishment of structural integrity and improved function *(1,3,25)*. Prolotherapy is thought to initiate a healing cascade that duplicates the natural healing process of poorly vascularised tissue such as ligaments *(6,12)*. Therapeutic interventions, such as prolotherapy that may enhance or speed up the connective tissue healing may be welcomed by the athlete and club medical staff *(16,23)*.

There is limited published evidence to support the use of prolotherapy in Achilles tendinopathy, osteoarthritis and generalised joint laxity however the effect of its use on AITFL or ATFL injuries in elite sportsmen is poorly documented *(12)*. This study reports on the results of prolotherapy used to treat ATFL and AITFL injuries in elite level athletes and describes the time to return to play (RTP) and rate of reinjury.

METHODS

Patients who had undergone prolotherapy treatment since February 2014 under the care of three specialist sports musculoskeletal radiologists for ankle sprains were identified using the patient database. Patients were found by initially searching for key words such as prolotherapy, glucose, P2G, ankle sprain, ATFL and AITFL. All positive results were then reviewed and only relevant patient files were then chosen. Patients were included in this study if they were elite athletes, the injury was acute, and there was no medial ligament involvement. The prolotherapy technique involved injecting a sclerosing solution (dextrose/sugar solution) into the injured ligament under ultrasound scan guidance by one of three experienced sports musculoskeletal radiologists.

A retrospective review of the patients medical and rehabilitation records was then carried out to collect the following information : age, gender, type of injury, number and timing of injections, technique used, content of injection, other injuries, other treatments, reinjury rate and return to play information. All players were considered 'injured' until club medical staff allowed full participation in training and availability for match selection *(9,10,17)*. Re-injury was defined according to the concept of early recurrences *(9)*, and any re-injury was documented. A literature review was carried out to identify the RTP times for conservative and surgical treatments of ATFL and AITFL injuries to allow comparisons with prolotherapy treatments to be made. Institutional review confirmed that formal ethics approval was not required as this study was an evaluation of service.

After the injection, all patients were advised to rest the ankle for 24 hours and they should then return to their normal rehabilitation program. Players were instructed not to use any form of boots such as an Aircast or camwalker and avoid NSAIDS due to the effect prolotherapy may have on platelets.

Standard rehabilitation protocols were then followed for each individual injury and managed by the individual clubs.

RESULTS

11 elite athletes were referred for ankle injuries between February 2014 and June 2018 that went on to have prolotherapy treatment. Of the cohort of athletes two had medial ligament injuries and were therefore excluded from the study. The mean age for the lateral ligament athletes was 23.7 years (range, 17-32). and the number of prolotherapy injections ranged between one and three with each one being one week apart (Table 1).

In our review of the prolotherapy treatment of grade III ATFL group RTP mean duration was 62 days (range : 38-87 days). The range has also been reported to allow comparison with published data

Table 1. — Demographic, injury and treatment of elite athletes included in our study.

Player	Age	Sport	ATFL Grade	AITFL Grade	No of Injections	RTP
1	27	Rugby	III	IIa	3	56
2	25	Football	III	NAD	3	55
3	22	Football	III	NAD	2	46
4	30	Rugby	NAD	IIa	1	66
5	22	Football	III	NAD	3	87
6	18	Football	II	NAD	2	38
7	20	Football	NAD	IIa	3	65
8	17	Football	III	NAD	2	51
9	32	Football	III	NAD	2	48

rather than using standard deviations. Regarding AITFL Grade IIa injuries treated by prolotherapy the mean duration was 62 days (range : 56-66 days). Importantly there was no evidence of any reinjuries in either the AITFL or the ATFL groups, which received prolotherapy. One case had mild pain exacerbation requiring simple analgesia, which improved within 24 hours. With the numbers available there were no significant difference between the outcomes of rugby and football players when reviewing RTP post prolotherapy results.

DISCUSSION

Since 1995, the definition of prolotherapy has changed *(25)*. The initial definition concentrated on the injection of inflammatory solutions to induce growth. However, as our understanding of the direct use of growth factors and multiple ways to stimulate them has improved, the definition of prolotherapy is best described simply as RIT, or more specifically 'the injection of growth factor production stimulants to promote regeneration of normal cells.'*(33)*. In the case of dextrose / sucrose injection the result is inflammation which involves release of multiple growth factors, which ultimately result in healing with scarring.

The most common prolotherapy agent used is dextrose, with concentrations ranging from 12.5% to 30% *(6)*. As it is water soluble and can be safely injected into multiple areas it is considered a good prolotherapy agent. Hypertonic dextrose solutions act by "dehydrating cells at the injection site, leading to local tissue trauma, which in turn attracts granulocytes and macrophages and promotes

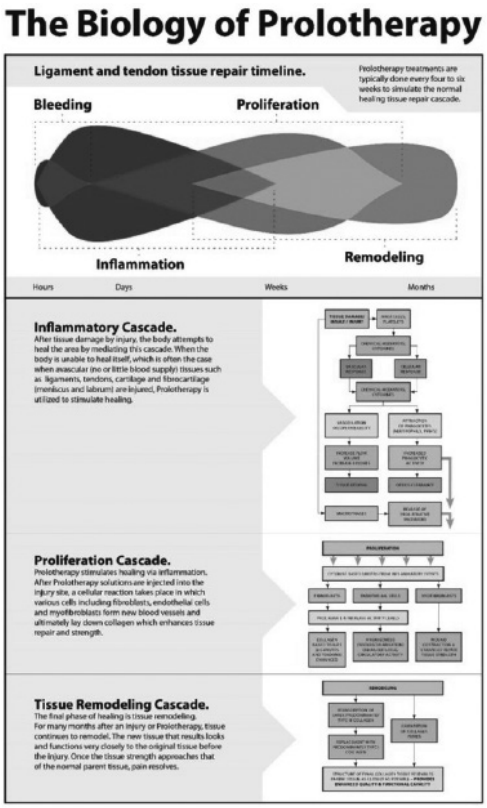


Figure 1. — The biology of prolotherapy. Prolotherapy induces the three stages of healing and restoration: inflammation, proliferation, and tissue remodelling. Used with permission from Ross Hauser, MD. www.CaringMedical.com

healing" *(12)*. This is a key part of the 'proliferation cascade' (Figure 1) *(28)*.

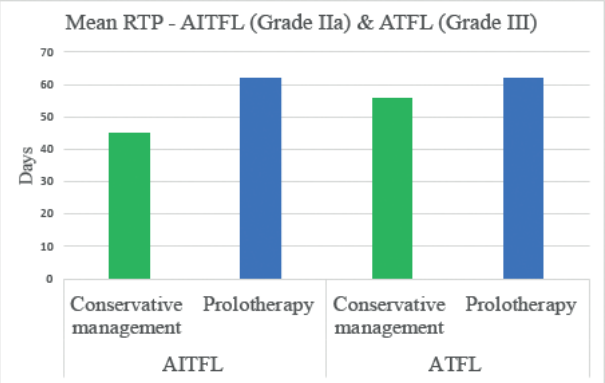
A normal human cell contains only 0.1% dextrose *(5)*. When exposed to an extracellular d-glucose (dextrose) concentration of as little as 1% human cells produce platelet-derived growth

factors inclusive of : transforming, beta, epidermal, basic fibroblast and connective tissue *(5,8,19-22)*. These growth factors are crucial for the growth and repair of tendons, ligaments and cartilage *(35)*. It has generally been accepted that 12.5% dextrose is the minimum concentration required to stimulate the inflammatory cascade and therefore enhance healing / growth effect *(26)*. However there is a lack of agreement between physicians regarding the optimal dose of dextrose, as was evident in the present study in which the dextrose injected varied, ranging from 25% to 30%. This variation is a weakness in our study.

When comparing the prolotherapy results presented here with those previously published without using prolotherapy in elite athletes the mean RTP for conservative management of ATFL injuries is 56 days (range, 42-120) compares favourably *(15,27)*. Mean RTP after surgical treatment for grade III ATFL ruptures has previously been reported at 72 days (range, 56-127 days) *(30,34)*. The comparison of mean RTP of nonoperative and prolotherapy treatment can be seen in Graph 1. For professional athletes with grade IIa AITFL injuries the mean RTP was 45 days (range, 23 to 63 days) in the present study, compared with 64 days (range, 27 to 104 days) for those with grade IIb injuries *(4)*. When comparing results for prolotherapy for the AITFL grade IIa in the present study the mean duration was less than the operative treatment time, but longer then the conservative treatment as can be seen in **Graph** 1.

One study looking at prolotherapy treatment in elite athletes with groin pain concluded that pain scores improved, and indeed 92% of patients were no longer restricted with regard to participation in sport *(29)*. However, to our knowledge, there are no reports in the literature on the results of prolotherapy for the treatment of ATFL or AITFL injuries in elite athletes prior to the present study.

Both the literature and the present case series demonstrate that prolotherapy is safe, with few adverse reactions, which can include mild pain or bleeding at the injection site. The development of a post-injection pain flare is usually self -limited and often resolves within one to two days *(24)*. In the present series only one case was affected. There was



Graph 1. — Return to Play Time- AITFL (Grade IIa) & ATFL (Grade III). This compares the prolotherapy RTP days compared to elite athletes not managed by prolotherapy.

no evidence if reinjury in either the AITFL or ATFL groups which had received prolotherapy treatment. This could be a significant factor to consider given that incomplete healing of these ligaments can lead to long term laxity, with resultant instability, loss of function, and an increased risk of reinjury and secondary injuries, such as to chondral surfaces *(31,36)*.

The weaknesses of the present study includes, the small sample size, the variation in the percentage of dextrose injected according to the radiologist undertaking the injection as described above, and furthermore that this was a retrospective review.

CONCLUSION

The case series shows that prolotherapy is a safe alternative treatment for ATFL and AITFL injuries in elite athletes. Additionally, it appears effective as no re-injuries were noted in the prolotherapy group. This is a significant finding that demands further data collection and assessment over a longer period. However our results in this small series have not demonstrated any improvement in RTP when using prolotherapy for the initial ATFL/AITFL injury when compared to similar injuries treated conservatively without prolotherapy.

To our knowledge this is the first study investigating prolotherapy treatment of ATFL/AITFL in elite athletes. Further clinical research assessing prolotherapy as a treatment for ligament injuries

is needed before it is possible to make specific recommendations including ideal protocols and optimal indications. This should be inclusive of long term follow up to include reinjury lost time.

REFERENCES

1. **Ada AM, Yavuz F**. Treatment of a medial collateral ligament sprain using prolotherapy : a case study. *Alternative Therapies Health Med.* 2015 ; 21 : 68-71.
2. **Angele P, Hoffman H, Williams A, Jones M, Krutsch W**. Specific aspects of football in recreational and competitive sport. *In : Prevention of injury and overuse in sports*. (Ed Mayr H, Zaffagnini S). London : Springer ; 2016 : 117-136.
3. **Banks AR**. A rationale for prolotherapy. *J. Orthop. Med.* 1991 ; 13 : 54-59.
4. **Calder JD, Bamford R, McCollum G**. Stable Versus Unstable Grade 2 High Ankle Sprains : A Prospective Study Predicting the Need for surgical Stabilisation and Time to Return to Sports. *Arthroscopy* 2016 ; 32 : 632-642.
5. **Di Paolo S, Gesualdo L, Ranieri E, Grandaliano G, Schena FP**. High glucose concentration induces the over-expression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. *Am. J. Pathol.* 1996 ; 149 : 2095-2106.
6. **Distel LM, Best TM**. Prolotherapy : a clinical review of its role in treating chronic musculoskeletal pain. *PM R* 2011 ; 3 : S78-81.
7. **Ekstrand J, Hagglund M, Walden M**. Injury incidence and injury patterns in professional football : the UEFA injury study. *Br. J. Sports Med.* 2011 ; 45 : 553-558.
8. **Fukuda K, Kawata S, Inui Y, Higashiyama S, Matsuda Y, Igura T, *et al.*** High concentration of glucose increases mitogenic responsiveness to heparin-binding epidermal growth factor-like growth factor in rat vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* 1997 ; 17 : 1962-1968.
9. **Fuller CW, Ekstrand J, Junge A, Andersen TE, Bahr R, Dvorak J, *et al.*** Consensus statement on injury definitions and data collection procedures in studies of football (soccer) injuries. *Br. J. Sports Med.* 2006 ; 40 : 193-201.
10. **Hagglund M, Walden M, Bahr R, Ekstrand J**. Methods for epidemiological study of injuries to professional football players : developing the UEFA model. *Br. J. Sports Med.* 2005 ; 39 : 340-346.
11. **Hagglund M, Walden M, Ekstrand J**. Injuries among male and female elite football players. *Scand. J. Med. Sci. Sports* 2009 ; 19 : 819-827.
12. **Hauser RA, Lackner JB, Steilen-Matias D, Harris DK**. A Systematic Review of Dextrose Prolotherapy for Chronic Musculoskeletal Pain. *Clin. Med. Insights Arthritis Musculoskelet. Disord.* 2016 ; 9 : 139-159.
13. **Hawkins RD, Fuller CW**. A prospective epidemiological study of injuries in four English professional football clubs. *Br. J. Sports Med.* 1999 ; 33 : 196-203.
14. **Hawkins RD, Hulse MA, Wilkinson C, Hodson A, Gibson M**. The association football medical research programme : an audit of injuries in professional football. *Br. J. Sports Med.* 2001 ; 35 : 43-47.
15. **Hubbard TJ, Hicks-Little CA**. Ankle ligament healing after an acute ankle sprain : an evidence-based approach. *J. Athl. Train.* 2008 ; 43 : 523-529.
16. **Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby R, Jr.** Early inflammatory response of knee ligaments to prolotherapy in a rat model. *J. Orthop. Res.* 2008 ; 26 : 816-823.
17. **Lundblad M, Walden M, Magnusson H, Karlsson J, Ekstrand J**. The UEFA injury study : 11-year data concerning 346 MCL injuries and time to return to play. *Br. J. Sports Med.* 2013 ; 47 : 759-762.
18. **Morgan BE, Oberlander MA**. An examination of injuries in major league soccer. The inaugural season. *Am. J. Sports Med.* 2001 ; 29 : 426-430.
19. **Murphy M, Godson C, Cannon S, Kato S, Mackenzie HS, Martin F, *et al.*** Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. *J. Biol. Chem.* 1999 ; 274 : 5830-5834.
20. **Oh JH, Ha H, Yu MR, Lee HB**. Sequential effects of high glucose on mesangial cell transforming growth factor-beta 1 and fibronectin synthesis. *Kidney Int.* 1998 ; 54 : 1872-1878..
21. **Ohgi S, Johnson PW**. Glucose modulates growth of gingival fibroblasts and periodontal ligament cells : correlation with expression of basic fibroblast growth factor. *J. Periodontal Res.* 1996 ; 31 : 579-588.
22. **Pugliese G, Pricci F, Locuratolo N, Romeo G, Romano G, Giannini S, *et al.*** Increased activity of the insulin-like growth factor system in mesangial cells cultured in high glucose conditions. Relation to glucose-enhanced extracellular matrix production. *Diabetologia* 1996 ; 39 : 775-784.
23. **Rabago D, Best TM, Beamsley M, Patterson J**. A systematic review of prolotherapy for chronic musculoskeletal pain. *Clin. J. Sport Med.* 2005 ; 15 : 376-380.
24. **Rabago D, Slattengren A, Zgierska A**. Prolotherapy in primary care practice. *Prim. Care* 2010 ; 37 : 65-80.
25. **Reeves KD**. Technique of Prolotherapy. *In : Phsyiatric Procedures in Clinical Practice*. (Ed Lennard TA). Philadelphia : Hanley and Belfus ; 1995 : 57-70.
26. **Reeves KD, Fullerton BD, Topol GA**. Evidence based regenerative injection therapy (Prolotherapy) in sports medicine. *In : The Sports Medicine Resource Manual*. (Ed Seidenberg PH, Beutler AI). Amsterdam : Elsevier ; 2008 : 611-619.
27. **Rezaninova J, Hrazdira L, Moc Kralova D, Svoboda Z, Benaroya A**. Advanced conservative treatment of complete acute rupture of the lateral ankle ligaments : Verifying by stabilometry. *Foot Ankle Surg* 2018 ; 24 : 65-70.
28. **Steilen D, Hauser R, Woldin B, Sawyer S**. Chronic neck pain : making the connection between capsular ligament

laxity and cervical instability. *Open Orthop. J.* 2014 ; 8 : 326-345.

29. **Topol GA, Reeves KD, Hassanein KM**. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Arch. Phys. Med. Rehabil.* 2005 ; 86 : 697-702.
30. **van den Bekerom MP, Kerkhoffs GM, McCollum GA, Calder JD, van Dijk CN**. Management of acute lateral ankle ligament injury in the athlete. *Knee Surg. Sports Traumatol. Arthrosc.* 2013 ; 21 : 1390-1395.
31. **van Rijn RM, van Os AG, Bernsen RM, Luijsterburg PA, Koes BW, Bierma-Zeinstra SM**. What is the clinical course of acute ankle sprains? A systematic literature review. *Am. J. Med.* 2008 ; 121 : 324-331 e326.
32. **Walden M, Hagglund M, Ekstrand J**. Time-trends and circumstances surrounding ankle injuries in men's professional football : an 11-year follow-up of the UEFA Champions League injury study. *Br. J. Sports Med.* 2013 ; 47 : 748-753.
33. **Warden SJ**. Cyclo-oxygenase-2 inhibitors : beneficial or detrimental for athletes with acute musculoskeletal injuries? *Sports Med.* 2005 ; 35 : 271-283.
34. **White WJ, McCollum GA, Calder JD**. Return to sport following acute lateral ligament repair of the ankle in professional athletes. *Knee Surg. Sports Traumatol. Arthrosc.* 2016 ; 24 : 1124-1129.
35. **Woo SL, Hildebrand K, Watanabe N, Fenwick JA, Papageorgiou CD, Wang JH**. Tissue engineering of ligament and tendon healing. *Clin. Orthop. Relat. Res.* 1999 : 367 : S312-323.
36. **Woods C, Hawkins R, Hulse M, Hodson A**. The Football Association Medical Research Programme : an audit of injuries in professional football : an analysis of ankle sprains. *Br. J. Sports Med.* 2003 ; 37 : 233-238.