

Hyaluronan injection therapy for athletic patients with patellar tendinopathy

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Abstract

Background Patellar tendinopathy produces activity-related pain and focal tenderness at the attachment of the patellar tendon at the lower pole of the patella. It frequently causes a reduction in athletic ability. An injection of hyaluronan was found to be useful for patellar tendinopathy, provided the indication is appropriate, based on the authors' pilot cases. The purpose of this study was to summarize the clinical experience of and to describe the appropriate indication for this injection therapy.

Methods Fifty patients were treated from January 1999 to December 2006. The observation period averaged 25.7 months (range 6–88). All patients were graded stage 2 or 3 by Blazina's classification. Each treatment was counted separately for 9 patients (10 knees) who had more than one treatment period with 3 months or more between the injections. There were 4 bilaterally injected patients. Patellar tendinopathy was classified into 4 types according to the degree of tenderness and the regions that are tender. Hyaluronan was injected into the interface between the patellar tendon and the infrapatellar fat pad at the proximal insertion, or into the region of maximum tenderness.

Results The total number of injections was 135, and there were an average of 2.0 injections per case (range 1–11). Following treatment, 54 % of the cases were rated in excellent condition, as they were able to return to their previous athletic activities with little difficulty, while 40 % of the cases were rated in good condition—these patients

were able to return to their previous sporting activities with some degree of limitation.

Conclusions Hyaluronan injection therapy for athletic patients with patellar tendinopathy is an optional but effective treatment.

Introduction

Anterior knee pain is one of the major causes of decreased sporting ability in athletes, and it can even cause an end to their participation in sports. It is especially frequently experienced by athletes who participate in sporting activities in which it is necessary to jump and twist the knee in flexion. Although the origin of this anterior knee pain is not clearly described or understood, the patellar retinaculum [1], medial parapatellar synovia [2], infrapatellar fat pad, [3] and patellar tendon have all been linked to anterior knee pain [4].

Patellar tendinopathy is well known as a difficult-to-treat condition among athletes who participate in sports that require frequent jumping [5, 6], but it is not well defined, and there is no consensus about its pathophysiology [7]. It is a common condition among athletes that is characterized by gradually progressed activity-related anterior knee pain and focal tenderness in the patellar tendon, with or without tenderness in the patella. The features of patellar tendinopathy that have been found by magnetic resonance imaging and ultrasound sonography include thickening of the patellar insertion site and even a partial tear of the posterior half at the insertion [8–10]. Repetitive impingement of the patellar tendon against the distal pole of the patella has been suggested as a cause of patellar tendinopathy [8]. The authors assume that degenerative changes in the posterior portion of the patellar tendon stimulate synovial tissue of the infrapatellar fat pad,

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which causes the pain associated with patellar tendinopathy (in a similar manner to how pain is generated in Achilles tendinopathy) [11].

Tenderness in the patellar tendon is frequently observed in athletic patients with anterior knee pain, and this has been reported to be an important diagnostic marker for physicians when diagnosing patellar tendinopathy [12]. We found that such tenderness usually exists only when the knee is in extension. When the knee joint flexes, the tenderness disappears in most cases. However, some patients show tenderness in the patellar tendon when the knee is in flexion as well as in extension. We refer to this kind of condition as “patellar tendinopathy” in a narrow sense, with particular treatment difficulties. In patients with this “patellar tendinopathy,” a lesion is hypothesized to exist in the posterior part of the patellar tendon at the patellar insertion [13]. In patients who only have tenderness in the patellar tendon in extension, the pain is thought to originate mainly from the infrapatellar fat pad. We have been performing management of athletic patients with anterior knee pain that is based upon the above-mentioned hypothesis. This kind of specification of patellar tendinopathy based on clinical findings has not been described before.

Hyaluronan injection therapy has been practiced for patients with knee osteoarthritis [14] and persistent shoulder pain [15] for more than 20 years in Japan. The safety and efficacy of hyaluronan therapy for patients with knee osteoarthritis has been established [16]. However, only one study in which this therapy was used to treat horse tendonitis has been reported in relation to the use of hyaluronan injection therapy for tendinopathy [17]. Clinical

experience of human patients with plantar fasciitis has been reported in Japanese [18], but there does not appear to be any such study in the English literature.

We have performed hyaluronan injection therapy for athletic patients suffering from long-standing pain or severe pain around the patellar tendon since 1999. Our hypothesis is that the local injection of hyaluronan is safe and effective for patients with patellar tendinopathy.

Materials and methods

All subjects gave their informed consent to participate in this study based on the efficacy and safety of hyaluronan and the favorable results of the therapy. When the patient's age was <20 years, the consent of their guardian was also required. Approval was given by the institutional review board (2009–0005) to administer hyaluronan injection therapy for patellar tendinopathy.

Subjects

Fifty patients (33 females and 17 males), with an average age of 26.4 years old (range 17–54), were treated in Tokyo Medical and Dental University Hospital from January 1999 to December 2006. No skeletally immature patient was administered hyaluronan therapy. The observation period averaged 25.7 months (range 6–88). Four patients were injected bilaterally (Table 1). When 3 months or more passed between injections, each injection was considered a separate period of therapy, as the patient returned to their

Table 1 Patient profile and number of periodically injected patients

Athletic level	Kind of sports	No. of patients (gender)	No. of periodically injected patients	Tegner activity score
Semiprofessional	Volleyball ^a	21 (3 males, 18 females)	5	8
	Baseball	5 (all males)	1	7
	Gymnastics	1 (male)		9
	Rugby football	1 (male)		9
Competitive	Judo	3 (all males)		9
	Speed skating ^b	1 (female)	1	7
	Downhill skiing	1 (female)	1	8
	Volleyball ^b	1 (female)		7
	Boating	1 (male)		7
	Rugby football	1 (male)		9
	Soccer	1 (female)		9
	Basketball	1 (female)		7
Recreational	Fencing	1 (female)		6
	Volleyball	7 (all females)		6
	Basketball	3 (all females)	1	6
	Baseball	1 (male)		5
	Kendo	1 (male)		5

^a Two patients with bilateral injection therapy

^b One patient with bilateral injection therapy

normal athletic activities during the interval. Even in the same patient, a different type of patellar tendinopathy was sometimes found during each treatment period.

Six patients who had undergone previous surgery in the ipsilateral knee were administered hyaluronan injection for their patellar tendinopathy. The surgeries that those patients had undergone were as follows: 3 ACL reconstructions (1 bone patellar tendon bone and 2 semitendinosus tendon reconstructions), 1 medial meniscus resection, and 1 medial and 1 lateral meniscus repair.

All patients were graded stage 2 or 3 by Blazina's classification [19]; that is, the patient suffered from pain during and after activity, and was unable to participate in sports to the same level as before the onset of pain. Patients suffered from knee pain for a minimum of 2 months with other conservative management approaches. An average of 9.0 months (range 2–60) had passed since the onset of the first episode of anterior knee pain before the hyaluronan injection therapy was initiated.

The patients had bilateral 4-direction radiography of the knee, including a tangential view of the patellofemoral joint, a weight-bearing anterior–posterior view in extension, a weight-bearing posterior–anterior view at 45°, and a lateral view in full hyperextension. The radiograph examinations showed that all but one of the patients were grade 0 or 1 according to the Kellgren–Lawrence osteoarthritis grading system.

Clinical classification according to the location of tenderness

Patellar tendinopathy in athletic patients was clinically classified into 4 types, which were defined based on the

region and position that was very tender, not according to the characteristics of the patient's complaints or MRI findings.

Type 1 was defined as tenderness in the proximal patellar tendon in flexion and extension. Type 2 was defined as tenderness in the parapatellar tendon region as well as the proximal patellar tendon in both flexion and extension. Type 3 was defined as tenderness in the patella itself as well as in the proximal patellar tendon in both flexion and extension. Type 4 was defined as tenderness in the parapatellar tendon region as well as in the patellar tendon, but only in extension.

Other types of anterior knee pain without maximum tenderness in the patellar tendon were not diagnosed as patellar tendinopathy, so they were not an indication for hyaluronan injection therapy in this study.

Injection methods and its indication

For “patellar tendinopathy,” hyaluronan was injected at the proximal interface between the posterior surface of the patellar tendon and the infrapatellar fat pad (Fig. 1). The needle was sometimes inserted from the front of the tendon perpendicular to the skin. When there was also tenderness in another region besides those associated with “patellar tendinopathy,” an additional injection into the other tender region was attempted in some cases. For patients with tenderness in the parapatellar tendon, injection into the portion with maximum tenderness was attempted. It was also important to select a layer in which the resistance to injection was minimal, with only minor complaints of pain from the patient during the hyaluronan injection.

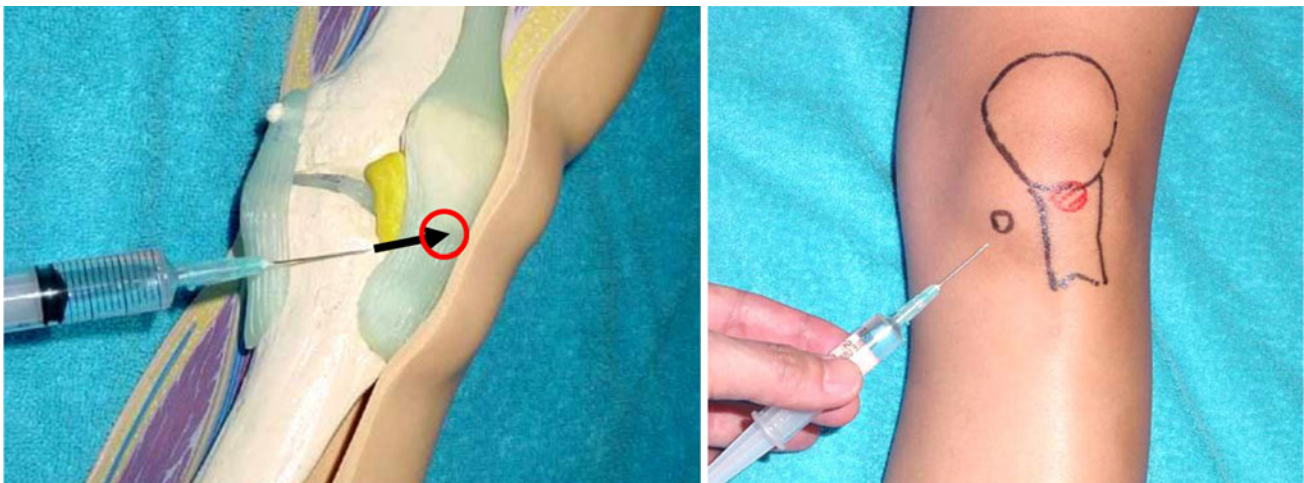


Fig. 1 Method used to inject hyaluronan at the interface between the patellar tendon and the infrapatellar fat pad. The patient extended the knee with full relaxation. An *open circle* was drawn on the skin medially from the medial border of the patellar tendon, and a *hatched circle* was drawn at the interface between the patellar tendon and the

lower pole of the patella. A needle was inserted into the open circle, aiming at the interface between the patellar tendon and the infrapatellar fat pad. A total of 2.5 ml of hyaluronan with 1 ml of 1 % lidocaine was usually injected with little resistance and little pain reported by the patient

An injection containing 25 mg of hyaluronan (molecular weight $\sim 900,000$ Da) in 2.5 ml (superpurified hyaluronate, Seikagaku Kogyo Co. Ltd., Tokyo, Japan) was used for the injection. After 2001, 1 ml of 1 % lidocaine was mixed with the hyaluronan in order to decrease the amount of dull pain experienced after injection.

The patient was asked to squat immediately after the injection in order to examine the effectiveness of the injection. After the injection, the patient's pain during squatting usually improved. Especially for patients with "patellar tendinopathy," it was important for the needle to be correctly inserted between the posterior margin and the infrapatellar fat pad (Fig. 2). A total of 3.5 ml of compound was easily injected in most cases with little resistance and only a few complaints of pain from the patients.

Hyaluronan injection therapy was only used in patients with patellar tendinopathy who had not been effectively treated with a standard conservative treatment for at least a 2-month period. Hyaluronan treatment was also attempted for patients with severe pain that made it impossible for them to continue participating in athletic activities as before. The interval between injections was at least 1 week. If an injection was sufficiently effective, another injection was done on the patient's request, despite the number of injections.

Combined therapy and restriction of athletic activities

The conservative treatment methods consisted of stretching the patella and parapatellar structures, and isometric quadriceps training. Squatting exercises were gradually increased as long as they were tolerated by the patient and their pain improved. Semiprofessional athletes had other

treatments (including ultrasound, electrical stimulation, and massage) from their trainers. Extracorporeal shock wave therapy was not performed in any patient [20]. If the patient felt good enough to return to their usual athletic activities with little pain after the injection, they were allowed to participate in activities (including a training game and a competitive game) soon after. Treatment with NSAIDs was not usually not subscribed because it is not effective for pain caused by patellar tendinopathy [7].

Evaluation methods

The effectiveness of the hyaluronan injection therapy was scored as one of four grades on the basis of subjective pain felt during sporting activities combined with a grade of recovery that reflected the patient's ability to participate in athletic activities. The scoring was done according to statements from both the patients themselves and their trainers according to a modified Roles and Maudsley score [21]. "Excellent" was defined as feeling no or little pain after the injection, which allowed the patient to successfully return to their previous sporting level. "Good" was defined as feeling an improvement after the injection, which allowed the patient to participate in the sporting activities that they did previously, albeit with some limitations. "Fair" was defined as the patient finding it difficult to return to the previous sporting level, despite some improvement after the injection. "Poor" was defined as the patient being unable to return to the previous sporting level with or without transient improvement after the injection.

We did not attempt to set any control treatment group because more than half of the patients belonged to a semi-professional team. MR images were also taken of some

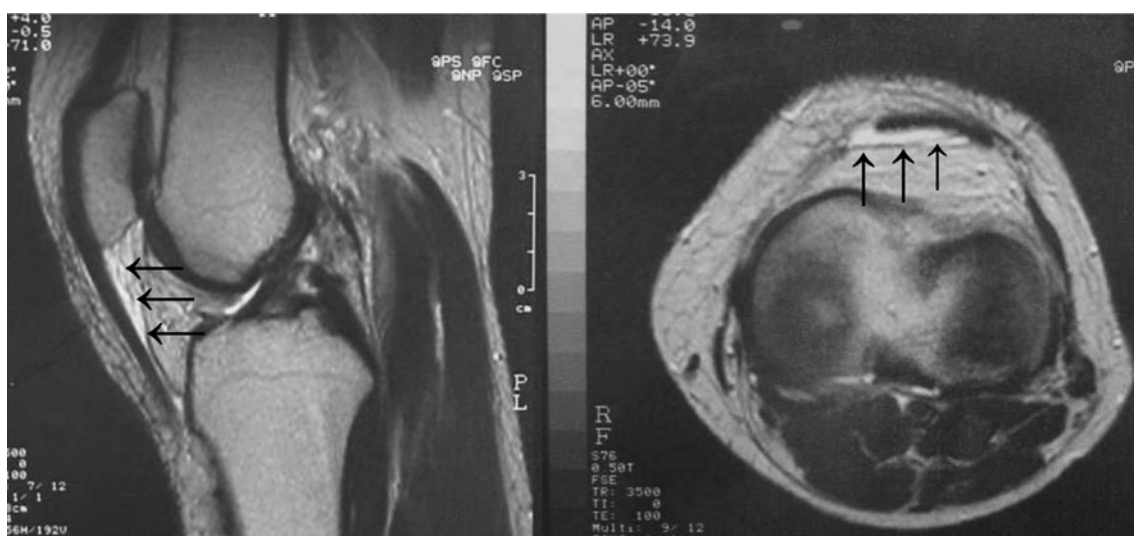


Fig. 2 Magnetic resonance images of the knee of a patient with patellar tendinopathy 4 h after hyaluronan injection. Both sagittal and transverse images reveal a high-intensity area between the patellar tendon and the infrapatellar fat pad, which indicates the presence of hyaluronan

patients to evaluate degenerative changes in the patellar tendon and other soft tissue as well as the patellar tendon to patellar junction.

Statistical analysis

The effectiveness of the injection therapy for patients in the four groups was analyzed statistically using the Kruskal–Wallis test. The Mann–Whitney *U* test was then used as a post hoc test. Significance was defined as a *p* value of <0.05. StatView for Windows (version 5.0) was used for the statistical evaluation (SAS Institute Inc., Cary, NC, USA).

Results

The total number of injections performed was 135, with an average of 2.0 injections per case (range 1–11) (Table 1). Among these, 10 knees (9 patients) had two or more injection therapies during the period of the study. The median interval between each injection was 12 months (range 3–49) (Table 2). Totally, 69 cases were experienced.

There was no case in which the hyaluronan injection was stopped during injection due to a complaint of pain from the patient. Almost all of the patients complained about dullness in the anterior knee region for one or two days following the injection, but they were usually able to perform athletic activities better than before the injection. All but one felt that the pain in the anterior knee region had improved. Some of them progressed with conservative management to a return to full athletic activities, while others were able to continue to participate in previous sporting activities. None of the patients decided to discontinue athletic activities due to pain in the anterior knee region after the hyaluronan injection therapy.

Figure 3 indicates the total number of injections for each case among the four clinical groups. Figure 4 shows the effectiveness of the hyaluronan injection therapy. The effectiveness of the therapy was found to be statistically significantly different among the groups. Hyaluronan injection was most effective for patients with “patellar tendinopathy” (type 1). The injection therapy was least effective in patients who only had tenderness in the patellar tendon in the extension position (type 4).

Discussion

The current clinical study suggests that hyaluronan injection therapy for patients with patellar tendinopathy is effective, safe, and repeatable. The clinical classification of patellar tendinopathy suggested in the study should prove

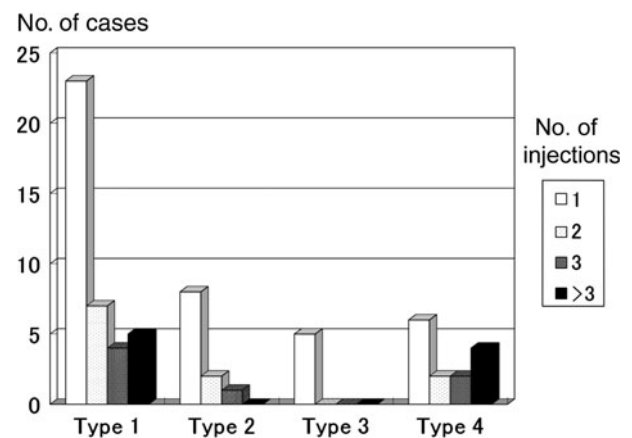


Fig. 3 Total number of injections for each case among the four clinical groups

Table 2 Detailed data on patients who received repetitive injection therapy

	Sports activity	Side	Total injection No. of cases	Effectiveness (no. of injections)			
				First case	Second case	Third case	Fourth case
1	Speed skating	Rt	2	Good (4)	Fair (5)		
2	Speed skating	Lt	2	Good (4)	Fair (5)		
3	Semiprofessional volleyball	Rt	4	Good (2)	Good (1)	Good (9)	Good (1)
4	Semiprofessional volleyball	Rt	3	Excellent (1)	Excellent (2)	Excellent (1)	
5	Semiprofessional baseball	Lt	2	Excellent (1)	Good (1)		
6	Competitive skiing	Lt	2	Excellent (1)	Good (1)		
7	Semiprofessional volleyball	Rt	3	Excellent (1)	Excellent (1)	Excellent (1)	
8	Semiprofessional volleyball	Rt	2	Good (1)	Good (1)		
9	Semiprofessional volleyball	Rt	3	Excellent (2)	Good (1)	Excellent (1)	
10	Recreational basketball	Lt	3	Good (4)	Good (1)	Good (1)	

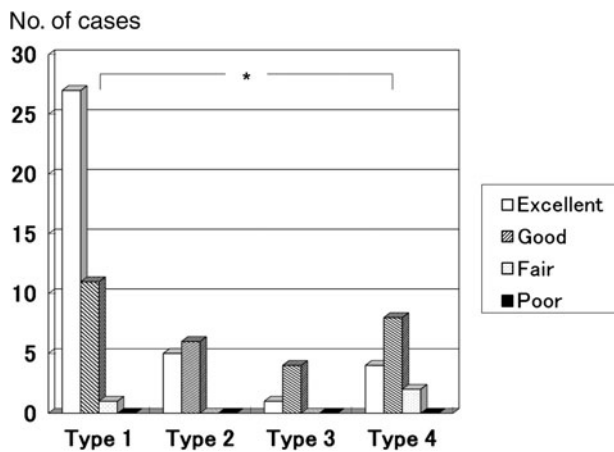


Fig. 4 Effectiveness of the hyaluronan injection therapy. Statistical analysis indicated that the four groups were significantly different

useful when considering hyaluronan injection for an athletic patient with anterior knee pain.

Tenderness in the patellar tendon of the knee in extension is noted in a significant number of athletic patients with anterior knee pain. Such tenderness in the patellar tendon usually disappears when the knee bends. When the knee is in flexion, the pressure on the infrapatellar fat pad is thought to decrease compared with when it is in extension, because the relatively hard structure of the femoral groove is on the back of the infrapatellar fat pad in extension [22]. Such clinical findings for athletic patients with patellar tendinopathy support the hypothesis that the infrapatellar fat pad is a significant source of pain [3]. A previous study by Dye et al. [23] indicated that the infrapatellar fat pad is a significantly painful structure in the knee joint in patients with patellar tendinopathy. The infrapatellar fat pad contains a significant number of substance P nerve fibers, as observed using histochemical analysis [24, 25]. The number of substance P positive fibers is reportedly well correlated with the pain experienced by female patients with ACL injuries [25].

We differentiated patellar tendinopathy in a narrow sense (“patellar tendinopathy”) from anterior knee pain syndrome in athletes. The results of this study of the injection of hyaluronan into the interface may support the hypothesis for the source of pain in “patellar tendinopathy.” The study of Romeo and Larson [26] may also support this hypothesis. They removed the posterior portion of the patellar tendon at the patellar insertion site arthroscopically, which resulted in an improvement in the level of pain experienced, which meant that the patient was able to return to their original athletic activities.

We speculate that the differences in the effectiveness of hyaluronan injection among the various types of patellar tendinopathy are due to different sources of pain, as follows. In type 1, the lesion is assumed to occur only in the

posterior portion of the proximal insertion of the patellar tendon. In type 2, the lesion is assumed to be present not only in the proximal insertion of the patellar tendon but also in the retinacular structure. In type 3, the lesion is assumed to occur not only in the proximal insertion of the patellar tendon but also in the patellar bone membrane. In type 4, it is assumed that the main lesion is in the infrapatellar fat pad and synovial structure. Given the nature of injection therapy, the effectiveness is assumed to differ among these four types because the liquid agent does not pass into the bone membrane. In type 4, since the lesion is not well defined, injection therapy will be indicated in only limited cases.

The safety and clinical usefulness of hyaluronan injection have been readily apparent throughout our 23-year experience in Japan. The rate of side effects from the injection therapy has been reported to be as low as 0.57 % (45 cases out of 7,845). Hyaluronan therapy was estimated to have been performed on 4,000,000 patients with knee osteoarthritis and on 500,000 patients with persistent shoulder pain in 2005. However, these data only refer to intra-articular injection.

Many kinds of high molecular weight hyaluronan are available in Japan for clinical use. High molecular weight hyaluronan has physical characteristics that make it a good joint lubricant, and it has also been reported to have an anti-inflammatory effect [27] and to promote tendon healing at the bone–tendon interface [28] as well as tissue regeneration [29]. Hyaluronan is also suggested to decrease sensory nerve sensitivity [30]. The favorable results of this therapy are thought to be achieved through hyaluronan’s promotion of tissue healing and anti-sense effects on the nerve. These multiple pharmacological effects could explain the favorable results of this injection therapy in patients with patellar tendinopathy.

We currently usually use 2.5 ml of hyaluronan combined with 1 ml of 1 % lidocaine in order to reduce local dull pain after injection, although no additional analgesia was included during the first 2 years of the study (1999–2000); during those first 2 years without additional lidocaine, the injection treatment gave excellent results in 60 % of the cases and good in 33 %, while excellent results were obtained in 54 % after 2001, and good in 43 %. The additional 1 ml of 1 % lidocaine does not appear to have any influence on the analgesic effects of the injected hyaluronan. The effects of injection were not always obtained in this study due a technical failure to inject. An ultrasound-guided technique would be helpful to solve the technical problem of injecting into the correct region [31].

A limitation of the current study is that it was performed retrospectively, with no control group. The evaluation methods are simple and subjective, but less objective. The athletic level of the patients was fairly high, and the main

purpose of the injection was to relieve pain safely and to return the patient to sporting activities as quickly as possible. Consequently, the evaluation was too subjective and not sufficiently precise. A randomized clinical trial is needed to confirm the effectiveness of the hyaluronan injection therapy for patellar tendinopathy.

Conclusion

Although this study may have several limitations regarding its design and the evaluation methods used, the results show that hyaluronan injection therapy for athletic patients with patellar tendinopathy is an optional but effective treatment.

Conflict of interest The authors declare that they have no competing interests.

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