ORIGINAL ARTICLE

Load management in tendinopathy: Clinical progression for Achilles and patellar tendinopathy

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KEYWORDS
Tendinopathy; Achilles; Patellar; Exercise; Load; Physical Therapy

Abstract  Achilles and patellar tendons are commonly affected by tendinopathy. Injury to these tendons can severely impact upon sports, recreational and everyday activities. Eccentric musculotendinous loading has become the dominant conservative intervention strategy for Achilles and patellar tendinopathy over the last two decades. Eccentric loading involves isolated, slow lengthening muscle contractions. Systematic reviews have evaluated the evidence for eccentric muscle loading in Achilles and patellar tendinopathy, concluding that outcomes are promising but high-quality evidence is lacking. Eccentric loading may not be effective for all patients (athletes and non-athletes) affected by tendinopathy. It is possible that in athletes, eccentric work is an inadequate load on the muscle and tendon. A rehabilitation program aiming to increase tendon load tolerance must obviously include strength exercises, but should also add speed and energy storage and release. The aim of this paper is to document a rehabilitation protocol for Achilles and patellar tendinopathy. It consists of simple and pragmatic exercises designed to incorporate progressive load to the tendon: isometric work, strength, functional strength, speed and jumping exercises to adapt the tendon to the ability to store and release energy. This article would be the first step for an upcoming multicentre randomized controlled trial to investigate its efficacy.
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Gestión de la carga en las tendinopatías: progresión clínica para tendinopatías de Aquiles y rotuliana

Resumen Las tendinopatías de Aquiles y rotuliana son muy frecuentes. Las lesiones en estos tendones pueden afectar severamente a las actividades deportivas, recreativas y cotidianas. En las últimas 2 décadas, los ejercicios excéntricos se han convertido en la principal intervención conservadora para tratar las tendinopatías de Aquiles y rotuliana. Los ejercicios excéntricos no son efectivos en todos los pacientes afectados por tendinopatías (atletas y no atletas). Es posible que en atletas, la carga que genera el trabajo excéntrico sobre el músculo y el tendón sea insuficiente. Un programa de rehabilitación que tenga por objetivo aumentar la tolerancia del tendón a la carga debe, obviamente, incluir ejercicios de fuerza, pero también debe agregar ejercicios de velocidad y ejercicios que aumenten la capacidad para almacenar y liberar energía. Este trabajo muestra un protocolo de rehabilitación para las tendinopatías de Aquiles y rotuliana. Consiste en ejercicios simples y pragmáticos diseñados para incorporar carga progresiva al tendón: mediante trabajo isométrico, fuerza, fuerza funcional, velocidad y ejercicios pliométricos que aumenten en el tendón la capacidad de almacenar y liberar energía. Este trabajo es el primer paso para diseñar un ensayo clínico aleatorizado y multicéntrico que permita evaluar su eficacia.

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Background

Achilles and patellar tendons are commonly affected by tendinopathy, which are overuse injuries characterized by localized tendon pain with loading and dysfunction.1-3 I understand tendinopathy as pain and dysfunction not related to the pathology, and knowing that there isn’t a direct connection between structure, pain and dysfunction, a classification based on the structure is called into question. The interaction between structure, pain and function hasn’t been completely understood. One can find regions in the tendon which are in different stages at the same time. The clinical presentation is a hybrid of reactive and degenerative pathologies, where the structurally ‘normal’ part (in the regular image modalities) has a reactive response, and there is a silent degenerative part of the tendon, mechanically and structurally incapable of transmitting tractive load, and this leads to overloading the normal part of the tendon. The tendon pain is partially related to the function, to the tendinopathy, diminishing muscle strength and motor control which, at the same time, reduces the function. The function in this context refers to the muscle’s ability to produce the appropriate strength so that the tendon can accumulate and release energy for the sports movements. However, one can find function changes when there is a structural pathology, independent from the pain.4

Both are common among athletes and Achilles tendinopathy may also affect sedentary people. Injury to these tendons can severely impact upon sports, recreational and everyday activities.1-3 The prevalence of patellar tendinopathy is high in sports characterized by high demands on speed and power for the leg extensors (i.e. volleyball and basketball).5 In the general population, the incidence of Achilles tendinopathy is 1.85 per 1000. In the adult population (21–60 years), the incidence is 2.35 per 1000. In 35% of the cases, a relationship with sports activity was recorded.6 Tendinopathy is commonly associated with tendon pathology. Pathological features of tendon pathology include altered cellularity (increased or decreased), break down in the extracellular matrix (ground substance accumulation, disorganized collagen, neurovascular ingrowth).7 Endocrine tenocytes and nerve endings release biochemical substances that are thought to have a role in tendon pain (e.g. substance P).8 Eccentric musculotendinous loading has become the dominant conservative intervention strategy for Achilles and patellar tendinopathy over the last two decades. Eccentric loading involves isolated, slow lengthening muscle contractions. Systematic reviews have evaluated the evidence for eccentric muscle loading in Achilles9-13 and patellar14,15 tendinopathy, concluding that outcomes are promising but high-quality evidence is lacking.16 Eccentric loading may not be effective for all patients (athletes and non-athletes) affected by tendinopathy.17 It is possible that in athletes, eccentric work is an inadequate load on the muscle and tendon. A rehabilitation program aiming to increase tendon load tolerance must obviously include strength exercises, but should also add speed and energy storage and release.18 The aim of this paper is to document a rehabilitation protocol for Achilles and patellar tendinopathy. It consists of simple and pragmatic exercises designed to incorporate progressive load to the tendon: isometric work, strength, functional strength, speed and jumping exercises to adapt the tendon to the ability to store and release energy (Fig. 1). This article would be the first step for an upcoming multicenter randomized controlled trial to investigate its efficacy.

The development of a rehabilitation plan for any individual with tendinopathy requires complex clinical reasoning, with reference to the pathoanatomical diagnosis and the functional requirements of the person. Tendinopathy and subsequent rehabilitation will vary considerably depending on the site of the pathology (i.e. insertion or...
mid-substance), the stage of the tendinopathy, functional assessment, fitness level of the person, contributing issues throughout the kinetic chain, comorbidities and concurrent presentations.\(^\text{19}\)

Scientific literature suggests that the pathogenesis of Achilles tendinopathy is heterogenic. Several risk factors and interactions between them have been identified. Both extrinsic (e.g. overuse) and intrinsic factors may predispose to injury.\(^\text{20-21}\) These include lipid levels, genes, metabolic disorders, age, circulating and local cytokine production, genre, biomechanics and body composition.\(^\text{22}\) It is crucial to have a holistic view of the patient and assess the risk factors.\(^\text{23,24}\) It is also important to take into account the total amount of load in the tendon, both at work and in sport.\(^\text{25}\) Understanding and addressing these factors may improve the outcomes.

The literature on the rehabilitation of tendinopathy suggests that the most important treatment is appropriate loading.\(^\text{26}\) The continuum model of tendinopathy\(^\text{27}\) provides a reasoned basis for considering targeted rehabilitation dependent on current clinical presentation.

Each component of the rehabilitation program, in particular loading, must be handled in relation to the nature, speed and magnitude of the forces applied to the muscle/tendon/bone unit in order to achieve the goals of the particular management phase, without causing exacerbation of the pathological state or pain. Exercise prescription can target matrix reorganization and collagen syntheses,\(^\text{28}\) reduce tenocyte activity, affect tendon compliance\(^\text{29,30}\) or have an analgesic effect.\(^\text{31}\) While matrix reorganization and improved collagen integrity are sometimes considered to be goals of the rehabilitation process, measurable structural change does not necessarily correlate with therapeutic outcome.\(^\text{32}\) There is reasonable evidence to refute observable structural change as an explanation of the benefits of eccentric work in tendinopathy.\(^\text{33}\) Exercise prescription may exert positive therapeutic effects through other mechanisms, such as change in mechanical properties of the tendon, functional strength, innervation, vascularity or perception of pain.\(^\text{34}\)

An accurate diagnosis is essential, imaging tests are helpful, but what really is important is a good clinical assessment. Based on the continuum model, we need to stage where the tendon pathology is: reactive tendinopathy, tendon dysrepair, degenerative or reactive on degenerative tendinopathy. The management of the load is the gold standard treatment at all stages. Early load management in a reactive tendon may keep them in the early stages of tendon pathology and limit the progression of their pathology.

**Key points to design and manage tendon load progression**

**Pain relief and balanced training**

1. Pain inhibits the athlete using the elastic (energy storage and release) capacity of the tendon, thereby compromising function and performance.\(^\text{35}\)
2. Excessive training volume or too intense training involving the elastic function of tendons may induce tendon overload and are important factors in the onset of athletic tendinopathy.
3. Repeated training combined with too short resting periods can result in a net degradation of the matrix and lead to overuse injury.\(^\text{36}\)
4. Managing tendinopathy in season centers around load management, these include strategies that control pain, both reducing aggravating loads and introducing pain-relieving loads.\(^\text{37}\)
5. No medication or injectable treatment to date has been shown to alter tissue properties; only tendon load can stimulate remodeling.\(^\text{38}\)
6. The only option for repeated failures to accommodate athletic load is a comprehensive rehabilitation program that can increase the load absorption ability of the tendon.\(^\text{39}\)
7. Loads that reduce pain should be introduced as early as possible. Loading to decrease pain will maintain a load stimulus on the tendon that is critical to maintain cell function and matrix integrity.\(^\text{40}\)
8. In painful (reactive, reactive on degenerative) tendons, isometric contraction with some load decreases pain for several hours.\(^\text{41}\) These loads can be repeated several times a day, using 40–60\(^\text{\%}\) holds, 4–5 times, to reduce pain and maintain some muscle capacity and tendon load.\(^\text{42}\) In highly reactive and painful tendons, bilateral exercises, shorter holding time and fewer repetitions per day may be indicated.\(^\text{43}\) Literature supports the use of isometric work in painful conditions; sustained isometric fatigue muscle contraction recruits segmental and/or extrasegmental descending inhibition mechanisms. The recruitment of descending inhibition results in mechanical hypoalgesia and increased pressure pain threshold in healthy individuals.\(^\text{44}\) Although there isn’t a golden standard for tendinopathy rehab,\(^\text{45}\) the guidelines (progression protocols) described in this article match the standards that other authors had previously presented and discussed.\(^\text{46,47}\) During the strength training sessions, the patients can use metronomes or phone apps, which provide a better control of the number of repetitions of each exercise. Adding these external stimuli has proven to maximize the effects of the workout and to prevent relapses\(^\text{48-50}\) and it must be taken into account.
9. Moderate to heavy loads with slow machine-based weights rarely cause pain. These exercises should be completed in the mid to inner range of the muscle-tendon unit to reduce compression at the tendon insertion.

Measuring tendon response to load

10. Provocative tests and objective scoring methods should be used to monitor tendon pain. As the VISA scales give substantial scores on pain during high-level activity, they are not responsive to short-term change and are best used on a month-to-month basis. Pain behavior the day after loading is the critical load response test. The athlete can monitor tendon response to training loads by completing a simple loading test every day at a similar time (avoid early morning except in the Achilles where morning pain and stiffness can be a good guide to progression).

11. Perhaps it is the magnitude of the structural tendon response to a load what matters, as this appears to occur before pain arises or changes. An instrument that could quantify the response of a tendon to load would mean a huge advance in the management of tendinopathy.

Prevention of tendon rupture. Evidence for changing tendon structure: aerobic training, synthesis of collagen and rest time

12. Kannus and Józsa examined 891 spontaneously ruptured tendons histologically and found that 864 (97%) of them had degenerative changes. If there’s degeneration and tendon overload for a prolonged period, the whole tendon can become degenerative and may fail completely. Avoiding these pathological changes is the main prevention to prevent rupture of the Achilles tendon. So, in addition to improving the pain and the functional-capacity load tolerance, we must maintain or improve tendon structure to prevent tendon rupture.

13. Mechanical loading seems to induce changes in gross morphology, mechanical properties as well as biochemical parameters of tendon tissue. It appears that both intense and regular exercise raise human collagen synthesis (Langberg et al., 1999; 2000; 2001; 2005; Miller et al., 2005), which suggests that human tendon tissue is more metabolically active in response to activity than what was previously believed. Intense exercise increased the formation of type I collagen during the recovery process, which suggests that intense physical loading leads to some kind of adaptation. Intense exercise in humans is followed by an increase of collagen synthesis and degradation. Over the first 24-36 h, this response results in a net loss of collagen, but this is followed by a net synthesis 36-72 h after exercise. An increased collagen synthesis is consistently observed as a part of the tendon adaptation response to mechanical loading, however the integration of new collagen into the matrix has not been shown. The COOH-terminal propeptide of type I collagen (PICP) is an indicator for collagen type I synthesis. PICP initially decreased after exercise and an increase in this marker of collagen synthesis was detected 72 h after exercise. In healthy humans, both synthesis and degradation increased after 4 week of physical training, whereas after 11 weeks only the collagen synthesis, and not the collagen degradation, was chronically raised.

The idea that the tendon can hypertrophy in response to mechanical loading suggests that there is a net formation of connective tissue. Both long-term (years) and relatively short-term (months) loading induce tendon hypertrophy. The degree of hypertrophy is rather small and seems to occur only in certain tendon regions. However, this appears to be true only in young people as collagen turnover after the age of 17 years is limited (Heinemeyer et al., 2011).

14. Persons who undergo regular training have a greater Achilles tendon cross-sectional area than other age-matched persons (Magnusson and Kjaer, 2003; Kongsgaard et al., 2005), which indirectly reflects a region-specific hypertrophy in response to long term loading, possibly during adolescent loading when the tendon is able to adapt structurally to load.

15. The potential region-specific adaptation to running appears to be far greater in men than in women. The ability of the tendon to adapt to regular loading is attenuated in women.

16. A similar increase in collagen synthesis is seen that is independent of exercise volume (repetitions), which suggests that there is a ceiling effect in collagen synthesis.

17. The fact that pro collagen expression is regulated the same way in the tendon regardless of the type of muscle contraction (eccentric, isometric or concentric) supports the belief that the collagen protein synthesis response is regulated by fibroblast strain.

18. With regard to tendon mechanical properties, increased tendon stiffness is generally observed in response to large volumes of loading.

Integrating structural effects of exercise into rehabilitation

19. Studies suggest that appropriate loading during rehabilitation of tendinopathy is the most important treatment method. Exercise prescription can target matrix reorganization and collagen synthesis, reduce tenocyte activity, affect tendon compliance or have an anabolic effect. The way the absorption of energy is distributed across the kinetic chain is important and each tendinopathy requires a holistic approach in terms of rehabilitation. Each component of the rehabilitation program, in particular loading, must be handled in relation to the nature, speed and magnitude of the forces applied to the muscle/tendon/bone unit in order to achieve the goals of the particular management stage (Table 1), without causing an exacerbation of the pathological state or pain. When planning a rehabilitation strategy, it is crucial to find an approach that addresses the re-education of muscle function instead as consider-
Table 1  Treatments and considerations for different tendinopathy stages.27

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive tendinopathy</td>
<td>Load management (reduction). Assessment and modification of intensity, duration, frequency and type of load is the key clinical intervention.</td>
<td>1. The tendon shows no adaptation to load → back to the load used before the symptoms</td>
</tr>
<tr>
<td>Tendon dysrepair</td>
<td>Process of adaptation to load → load management and exercise.</td>
<td>2. Isometrics Progression of strength work: Isometrics</td>
</tr>
<tr>
<td>Degenerative tendinopathy</td>
<td>Process of adaptation to load → load management and exercise.</td>
<td>3. Slow dynamic functional work (first progressing the strength, then the speed)</td>
</tr>
<tr>
<td>Reactive on degenerative</td>
<td>Settle the reactive tendon first and then address the degenerative component</td>
<td>4. Progressing the compression High load elastic (plyometric work)</td>
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<tr>
<td></td>
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<td>5. Energy storage and release loads</td>
</tr>
</tbody>
</table>

6. At the end of the progression the athlete should be able to use the elastic capacity of tendon and have regained function of the kinetic chain suitable for performance

Methods that lead to goal achievement according to key point

1. Load management (reductions) removes the cause of reactive or reactive on degenerative tendinopathy.13 Assessment and modification of the intensity, duration, frequency and type of load is the key clinical intervention.21 Intensity seems to be the most important feature; therefore this is the first factor we should modify by reducing intensity peaks (i.e. sprinting, sets, Fartlek, fast changes of direction, explosive jumping). Frequency is a very flexible value that we can use to adapt the load (more or less resting hours between workouts depending on the pain level of the next day). Volume seems to be the less aggressive feature, if there is enough time of rest among workouts, therefore at early stages we can keep the volume of training and change intensity and frequency. If pain increases the day after the workout we need to assess if the person should maintain regular training or adapt their training. Sometimes the athlete may need a different approach than the rest of the group (alternate days, half track, specific work, ...). The change on the Numeric Pain Scale (NPS) value the day after the workout tells us if the load is tolerated. Daily NPS: NPS should not raise on the loading test the day after training.

Effect of loading on tendon. Goals according to key points

1. Removing the cause of reactive or reactive on degenerative tendinopathy (usually unaccustomed load)
2. Reduce the pain through reduction of high loads
3. Introducing isometric loads that reduce pain at early stages
4. Adapt the training volume and resting periods to the amount that the tendon can safely handle at that moment
5. Increasing load capacity of the tendon up to that required by the person by improving the structural and/or mechanical properties of the tendon

ing the tendon as an isolated unit. While early stimulus of the muscle tendon unit is typically focused on isometric muscle activation, which may include muscle stimulation, most programs advocate the progression to higher loads as guided by symptom presentation.19 Progression beyond the early isolated strength and hypertrophy loading requires functional conditioning of the muscle-tendon unit, adjusting tendon load through faster eccentric work prior to starting skill specific re-education such as landings, before introducing sports specific challenges such as sprinting and cutting.19 Consideration of the cortical effects of exercise on the motor cortex are critical.
2. Isometric exercises reduce the pain in the early phase of rehabilitation or while managing an athlete in season. Isometrics must be heavy (up to 70% maximal voluntary isometric contraction) for the musculotendinous unit and be held for a long time (up to 45 s). 51,52

3. How the tendon responds to the training volume and rest periods indicates if the amount of load is within the load that the tendon can safely handle. During early stages of rehabilitation high energy storage loads should not be repeated in less than 48 h. Adapting the training according to the NPS observed the next day: If NPS increases keep 72 h rest between workouts, if NPS does not increase, keep 48 h rest between workouts, if NPS decreases it is possible to increase the frequency or intensity of high load training.

4. To increase load capacity of the tendon up to that required by the person by improving either structural or mechanical properties of the tendon, we must increase load absorption ability of the musculotendinous unit and the kinetic chain, through progressive loading. Mechanical properties of tendon, including tendon compliance, are improved later in rehabilitation by retraining landings, running, changing pace or direction, jumps (energy storage loads). Eccentric exercises incorporated in all the loads proposed in this paper seems to be the best way to stimulate remodeling of tissue.

5. The ultimate goal is that the athlete should be able to use the elastic capacity of tendon and have regained function of the kinetic chain suitable for performance. Functional exercises and individual technical exercises that involve high loads at maximum speed, to apply high force and achieve high velocity, maximum expression of force in sports where tendon have to show their ability to store and release energy in functional and asymptomatic form.

### Monitoring effect: load dosage and pain management according to pain level the day after the training Numeric Pain Scale (NPS)

Numbered scale from 0 to 10, where 0 means lack of pain and 10 the highest imaginable level of pain. The patient chooses the level that better suits his symptoms, knowing that 7 means an exaggerated pain resulting in modified function. It is essential to correlate pain during training with change on the loading test the next day (Table 2).

### Exercises progression

This is an example of progression, which would vary depending of the goals of each patient. Goals are different for an elite volleyball player and a weekend warrior. The program must be unique to each individual, since the needs of each person are also unique. The highest demanding parts of this program only apply to high performance level of competitive sports (Table 3).

1. On early stages, we keep a daily isometric work: 4–5 isometrics, holding 40° (from 30 to 60°) and resting at least 1 min and up to 2 min between each, 3 times a day. High loads provide best results. The load needs to be high but avoid muscle fatigue. Muscle vibration during

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**Table 2** Numeric pain scale and its correlation with training intensity.

<table>
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<tr>
<th>Training intensity</th>
<th>0</th>
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<td>No pain</td>
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<td>Intense pain, resulting in modified function</td>
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<td>Excessive training intensity</td>
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<td>Highest pain</td>
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**Table 3** Example daily monitoring and evolution of pain.
the execution of the exercise means that we are approaching fatigue and that the load is excessive. The exercise needs to be stopped at that moment and we will take that time (being 20°, 30°, 40° or any other amount) as a reference for progression.

Do I feel pain for the next few hours? No = maintain and gradually increase the time you hold the isometric contraction or the load if I stay below or equal to pain level 4 for 2 or 3 days. Yes = reduce the time you hold the isometric contraction

2. Progression: start slow isotonic exercises on alternate days. 4 sets of slow concentric- eccentric, 6–8 repetitions of 4″ concentric + 4″ eccentric. Increase the load (2 kg, 4 kg, 6 kg–12 kg). Rest 30″ between sets. Once a day, on alternate days. We keep the isometric work, alternating slow dynamic exercises (one-day isometric work, next day slow dynamic work, next one isometric, …)

Do I feel more pain the next day? No = increase the load in slow dynamic exercises every 2 or 3 days when I stay below or equal to pain level 4 for 2 or 3 days. Yes = reduce the load in slow dynamic exercises

3. Then increase the speed with functional exercises when base strength is adequate

Do I feel more pain the next day? No = increase the speed in functional exercises every 2 or 3 days when I stay below or equal to pain level 4. Yes = reduce the speed in functional exercises.

Maintain the strength exercises

4. Progression: add fast dynamic exercises every three days. 3 sets of fast concentric- eccentric contraction (explosive), 6–8 repetitions. Rest 2 min among sets. Once a day, every three days. Alternating fast dynamic work with slow dynamic and isometric work. (One day fast dynamic, the next day slow dynamic, the other day isometric, then again fast dynamic, …)

Do I feel more pain the next day? Yes = reduce the number of energy storage exercises. No = increase the number of energy storage exercises every 5–6 days

Maintain the strength exercises

Discussion

Achilles and patellar tendinopathy are the most common tendinopathies of the lower limbs. The ideal treatment to manage these tendinopathies doesn’t exist. There is a need for further research to resolve which is the best therapeutic strategy to help those patients who suffer from tendinopathies.

On the other hand, there is a number of effective exercise programs for Achilles and patellar tendinopathies. Eccentric training is the most commonly used. It was first posed by Alfredson et al. Systematic reviews have evaluated the results of eccentric loading of the injured tendon in tendinopathy, concluding that outcomes are promising, but high-quality evidence is lacking.

In our experience, the results obtained by athletic patients (professionals and nonprofessionals) in an isolated eccentric exercise program are poor.

Mallassaras et al. performed a systematic review of studies comparing two or more loading programs for Achilles and patellar tendinopathy. His conclusions recommend bearing in mind the eccentric and concentric exercises.

There are studies that recommend a Heavy Slow Resistance (HSR) program to treat lower limb tendinopathy. Keep in mind that the eccentric-exercise training is slow lengthening of a muscle-tendon unit while it is under load and Heavy-slow resistance training is a series of exercises in which each repetition is performed slowly (>6 s) for both the eccentric and concentric phase. In these studies, the HSR program achieved the same pain and function improvement (VISA score) than the Alfredson eccentric program, but with a significantly higher patient satisfaction at the six months follow-up. This clinical improvement came with a collagen rise in the HSR group. This data allows us to recommend the HSR program as an alternative to the eccentric workout for Achilles and patellar tendinopathy rehab.

Isometric exercises have been recommended to reduce and treated patellar tendon pain and to initiate muscle-tendon unit loading when the pain limits the ability to perform isotonic exercises. Five repetitions of 45-s isometric mid-range quadriceps exercise at 70% of maximal voluntary contraction have been shown to reduce patellar tendon pain for 45 min after the exercise and this was also associated with a reduction in the motor cortex inhibition of the quadriceps that was associated with patellar tendinopathy.

Some authors recommend including functional activities (like speed and leap exercises) in the tendinopathy rehab protocols for athlete patients. But they haven’t been implemented in the scientific literature yet.

In this sense, the progressive exercises protocol presented in this article takes into account the isometric and strength exercises (concentric and eccentric). The innovation resides in the incorporation of functional strength exercises, speed and leaps to adapt the tendon to the ability to store and release energy. In our clinical experience, incorporating these exercises is very important for the patellar and Achilles tendinopathy rehab for athletic patients.

Conclusion

This protocol can be useful to improve symptoms and function in Achilles and patellar tendinopathies. We have shown the exercises and their progression, we have been using this protocol in our clinical practice for the past 7 years. Our patients get positive results. But this is just a protocol. Randomized clinical trials are needed to demonstrate its efficacy, to devise an adequate dose-response model and to determine its long-term effects.
Conflict of interests

Authors declare that they don’t have any conflict of interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.apunts.2017.11.005.

References


