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Study design

Low-load exercise program and platelet-rich plasma for intrasubstance tear in lateral elbow tendinopathy: protocol for a double-blinded randomized clinical trial

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ABSTRACT:

Background: Lateral elbow tendinopathy (LET) is one of the most common musculoskeletal conditions. Treatment includes a series of therapeutic alternatives. However, the resolution takes nearly 24 months. Platelet-rich plasma (PRP) is an effective option, especially when the tendon presents an intrasubstance tear (IST). It is unknown what type of rehabilitation plan is more effective after this treatment. Aim**:** To perform a study protocol of a double-blinded, randomized clinical trial to determine the efficacy of a specific low-load exercise program in patients with LET and IST treatment with PRP under US-guided

Methods: A single-center, parallel-controlled, randomized, double-blinded, phase III trial was proposed. Patients over 18 years-old diagnosed with LET and IST treated with US-guided PRP will be selected. Two arms of treatment will be allocated with a ratio a 1:1 ratio (low-load exercise protocol vs. conventional exercise program). The principal outcome will be the reduction of the tendon tear size. Secondary outcomes will include Patient-Rated Tennis Elbow Evaluation score, visual analogue scale, and handgrip at baseline, 3, 6, and 12 months of follow-up. Statistical tests will be 2-sided t-test with an alpha level (significance level) of 0.05.

Discussion: The intervention aims to significantly reduce tendon tear size and improve pain and functionality in patients with LET and IST treated with US-guided PRP. We proposed one of the first studies in the literature that considered a detailed standardized exercise protocol applied to these patients. The result could be used to speed up treatment save time and money, help evaluate guidelines, and improve patients' and athletes' quality of life.

Keywords: Exercise program, lateral elbow tendinopathy, platelet-rich plasma, tendon tear, tennis elbow.

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Introduction

Tendinopathy describes a spectrum of changes in damaged and diseased tendons, leading to pain and reduced function (Millar et al., 2021). Lateral elbow tendinopathy (LET) is one of the most prevalent disorders of the arm (Shiri, Viikari-Juntura, Varonen, & Vaara, 2006), particularly in working populations (involving loaded and repeated gripping and/or wrist extension activities) (Sanders et al., 2015) and sports that involve racquets, vibrations, and eccentric impacts (Mohandhas et al., 2016).

Patients present severe pain over the humeral insertion of the common extensor tendons. Additional symptoms include loss of grip strength and functional disability during daily activities, such as grasping objects, turning doorknobs, and shaking hands (Lai, Erickson, Mlynarek, & Wang, 2018), impacting patients' quality of life and requiring direct medical spending (Sanders, Maradit Kremers, Bryan, Ransom, & Morrey, 2016).

Like other tendinopathies, LET has multiple therapeutic interventions with different effects. Among them are pharmacotherapy, physiotherapy, manual therapy, exercise, and educational strategies (Coombes, Bisset, & Vicenzino, 2015).

Emerging autologous cellular therapies that utilize platelet-rich plasma (PRP) preparations have recently gained increasing popularity with widespread use in diverse medical fields. The applications have the potential to play in a variety of regenerative medicine treatment plans (Everts, Onishi, Jayaram, Lana, & Mautner, 2020a). This therapeutic application stimulates repair mechanisms and restore function in damaged body tissues as tendinopathies (Costa-Almeida, Calejo, & Gomes, 2019) (Liu, Hindieh, Leong, & Sun, 2017).

PRP uses different methods and forms of preparation for its use (Trebinjac & Nair, 2020). A review published in 2014 demonstrated the differences between volume, platelet count, cell type, number of centrifugations, time, and temperature, among many other factors (Dhurat & Sukesh, 2014). It is possible that this will have an effect on the healing process. For this reason, it is essential to use the same instruments, dosage, and form of administration. One therapeutic alternative is ultrasound (US)-guided PRP injection for the treatment of this condition. It is a safe, minimally invasive, and effective procedure in improving the sonographic and pathological changes of the common extensor tendon (CET) (Khattab & Abowarda, 2017), with good long-term follow-up results (Alessio-Mazzola et al., 2018) Figure 1.

There is level 1 evidence to support the efficacy of a single injection of US-guided PRP for the treatment of tendinopathies. The preparation and

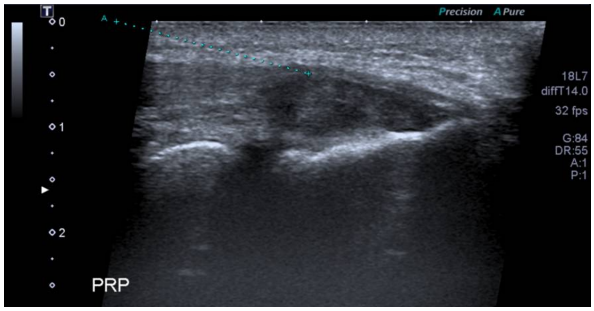

Figure 1. Platelet rich plasma US-guided. Using an aseptic technique and prior local anesthesia in the cutaneous and subcutaneous planes, puncture is performed, infiltration of PRP in a volume of 5 cc, distributed at the level of the extensor tendon origin, in addition to multiple fenestrations at this level.

intratendinous injection technique of PRP appears to be of great clinical significance (Fitzpatrick, Bulsara, & Zheng, 2017). However, there is no consensus on optimal rehabilitation protocols after PRP treatment for musculoskeletal disorders, even though basic science studies suggest clear roles for physical therapy and mechanical loading in the restoration of tendon structure post-PRP injections (Neph et al., 2020) (Everts, Onishi, Jayaram, Lana, & Mautner, 2020b).

On the other hand, the majority of exercise rehabilitation programs are based on eccentric exercise therapy (EET) in patients with tendinopathies, particularly LET. A meta-analysis published in 2021 concluded that eccentric exercise can improve pain and muscle strength in patients with LET (Yoon et al., 2021). Moreover, another recent systematic review of high-quality randomized controlled trials studied the efficacy of eccentric strengthening compared with other forms of strengthening and pain-relieving modalities on strength, function and pain in people with LET, with controversial results (Chen & Baker, 2021). It has also been reported that lower impact loads on the tendon could be beneficial.

Recently, a randomized clinical trial concluded that low-load progressive exercise is more effective than traditional eccentric exercises (Breda et al., 2021). No publications evaluate the effectiveness of a low-load standardized protocol in patients with intrasubstance tear of the tendon origin of the wrist extensors associated with a platelet-rich plasma procedure under ultrasonography.

We hypothesize that low-load exercise significantly enhanced tendon repair in patients with LET after a PRP procedure. Therefore, this study aims to evaluate the efficacy of a low-load exercise (stretching) protocol vs. a traditional rehabilitation program in patients diagnosed with LET with IST treated with

platelet-rich plasma infiltration under guided ultrasonography.

Materials and Methods

Study Design

The current study protocol is a single-center, parallel, block-randomized using a 1:1 allocation ratio, controlled, double-blinded, phase III trial to evaluate the superiority of a specific low-load exercise training protocol in tendon tear size in patients with LET treated with PRP US guided injection.

Study Setting

Our clinic is one of the most important medical sports centers in Latin America, with more than 350,000 physical therapy appointments per year. Considering a prevalence of LET of around 3–8% in the general population (Degen et al., 2018), we will recruit our patients because we acknowledge that our institution is optimal for developing this trial. Furthermore, an intrasubstance tear in LET represents nearly 1/3 of all ultrasound findings (Droppelmann et al., 2022) and, nearly 25% of our patients with LET and IST are treated with PRP.

Reporting

This article followed the Consolidated Standards of Reporting Trials (CONSORT-Statement) (Schulz, Altman, & Moher, 2010). The CONSORT 2010 statement comprises a 25-item checklist addressing a minimum set of recommendations for reporting randomized trials. The checklist is available in (consort-statement).

Research Question

The research question was to evaluate the efficacy of a low-load exercise (stretching) protocol vs. a traditional rehabilitation program in patients diagnosed with LET and IST treated with Leucocyte rich platelet-rich plasma (LR-PRP) infiltration under US-guidance. Primarily, we will evaluate the reduction of tendon tear size using the diagnosis US. Secondly, we estimate a clinical reduction in the patient-rated tennis elbow evaluation (PRTEE). This questionnaire has been recently recommended by the 2022 consensus statement (Bateman et al., 2022), and is the most commonly used LET questionnaire in the literature. The first item is pain in the affected arm using a visual analogue scale of pain from 0 (no pain) to 10 (worst imaginable pain). The second item consider functional activities divided into specific and usual. Both sub items were used and scaled from 0 (no difficulty) to 10 (unable to do) (Evans et al., 2019). The following PICOT (Participants, Interventions, Comparison, Outcome, and Time) criteria were used, Table 1.

Table 1. PICOT strategy for this study

Participants

Inclusion Criteria

Acronym	Component	Explanation
(P)	Population	Patients over 18 years of age, regardless of gender, race, or ethnicity, with a clinical and US diagnosis (imaging and functional tests) of LET with IST and under first dose, 5 ml of volume of LR-PRP injection US-guided.
(I)	Intervention	Low-load exercise (stretching) for patients with LET and IST.
(C)	Comparison	Patients under a traditional and standardized rehabilitation program.
(O)	Outcome	*Reduction in tendon tear size using ultrasonography (Hayes et al., 2019) . **Reduction in the PRTEE score. The clinical significance was defined as a reduction of 22% of the baseline score (Poltawski & Watson, 2011).
(T)	Time	The follow up was 12 months.

IST: Intrasubstance tear; **LET:** Lateral elbow tendinopathy; **LR-PRP:** Leucocyte Rich Platelet-rich plasma; **PRTEE:** Patient-Rated Tennis Elbow Evaluation; **US:** Ultrasound; *****: Primary outcome; ******: Secondary outcome.

Patients will be included if they have the following criteria: (i) 18 years of age and up with a medical and imaging diagnosis of LET and IST; (ii) treatment under LR-PRP in our institution; (iii) Physical Therapy derivation after 3 weeks of the LR-PRP procedure; (iv) capability to express both pain and functionality; (v) ability to respond to the PRTEE score and make an elbow US; (vi) sign the informed consent form; (vii) willingness and ability to maintain a six-month follow up.

Exclusion Criteria

Patients will be excluded if they have the following criteria: (i) patients who have had LET surgery or elbow prosthesis; (ii) any hematologic condition; (iii) chronic systemic corticosteroid use (>3 months in the past 12 months); (iv) radial tunnel syndrome; (v) treated with intratissue percutaneous electrolysis; (vi) pregnancy and./or lactation; (vii) hypertension that is uncontrolled, as well as a history of hypertensive crisis; (viii) history of arrhythmia, decompensated heart failure, coronary artery disease; (ix) ischemic stroke, neurovascular disease or hemorrhage, severe head injury, hydrocephalus, and increased intracranial pressure; (x) history of uncontrolled or untreated primary or metastatic malignant brain lesions; (xi) severe psychiatric illness with psychosis/hallucination (e.g., schizophrenia,

acute psychosis); (xii) history of alcohol abuse and drug abuse/dependence; (xiii) subjects who are scheduled to have surgery during the study period; (xiv) patients who are starting chemotherapy; (xv) patients diagnosed with COVID-19 infection in the last 3 months.

Interventions

The selected patients will be referred to the physical therapy department and randomized to intervention (group A) or control (group B) arms. All eligible patients will sign the informed consent form in the first session, and the most essential clinical and sociodemographic variables will be recorded. Tendon size and tear will also be measured with US, and the PRTEE questionnaire will be used. Anamnesis and wrist flexion, extension tests, and handgrip using dynamometers were included. Electrotherapeutic modalities such as interferential current (IFC) (Fuentes, Olivo, Magee, & Gross, 2010), and thermotherapy (TT) hot and warm compresses (Bin, Cimin, Li, Wang, & Chen, 2022) are included in both groups when they begin the session in the first 12 minutes.

Group A will participate in Clínica MEDS La Dehesa (CMLD) on AM shift. We designed a specific rehabilitation program based on progressive low-load exercises three times a week. Mostly, we included different stretching exercises for the elbow, wrist, and fingers. Also, we included sliding exercises for the ulnar and radial nerves. A little progression was designed every three treatment sessions. The complete detailed exercises are in Appendix 1 (Figures 1 to 11).

On the other hand, Group B will participate in Clínica MEDS CMLD on PM shift for the purpose of meeting the blind participants. We considered standardized exercise recommendations of three times a week following the recommendations of a standardized strength program for the wrist and scapular region (Day, Lucado, & Uhl, 2019). The IFC and TT were the same as in Group A. However, the exercise program is based on muscle contraction using progressive strengthening exercises, mobilizations with movement, and cryotherapy for 5 minutes at the end of the session. The complete detailed exercises are also in Appendix 1 (Figures 12 to 42).

Sample Size

For the primary outcome, a reduction of at least 80% of tendon size was proposed to measure the impact of a low-load exercise program on LET patients with IST under US-guided PRP. A test of differences in proportions was used to consider a large effect size, assuming a binomial distribution through an arcsine function, using a power of 80% and a p-value of 0.05 with a two-sided test. The estimated number of participants per group is 24,5. Therefore, 25 patients per group are needed. The loss is estimated to be 20%. The final size is 60 participants (30 per group). However, considering this is a phase III study, and the intervention proposed is safe, we will double our sample size estimation to 120 patients (60 per group).

Recruitment

The sampling process will be through a non-probabilistic strategy. The process will be carried out in a reference medical center in Latin America, located in Santiago de Chile, whose specialty is traumatological and orthopaedic injuries. The subjects will be found when they go to their medical appointments with their treating professionals. After the PRP-US guided procedure, they are usually sent to physical therapy sessions.

Detection will continue until the target sample size is reached. Recruitment will be monitored by the clinic's hand and elbow unit.

Randomization

After approval by The Ethics Committee, eligible patients will be randomly allocated as clusters in a 1:1 ratio to one of the two treatments arms. The randomization sequence will be computer-generated using the R package randomizeR for clinical trials (Uschner, 2016).

Participants will be randomly assigned to the intervention or control group according to the therapeutic behavior of the treating physician. The research fellow will be in charge of the distribution process and will have access to the allocation. The other researchers will only have access to case-identifying sequential numbers.

Blinding

Randomization will be determined by the appointments made by the physicians responsible for the patients for physical therapy treatment at any of the shifts. They will be unaware of the research and, as a result, will be unaware of which type of experimental or control intervention will be carried out, which will have no bearing on the decision to refer patients to the rehabilitation process. In this sense, we have decided that each shift will have a form of treatment for each of the two intervention groups. In this way, the bias of confusion or mixture of effects between the participants is avoided. Therefore, we will compare interventions by treatment shifts. This study consisted of a double-blinded strategy (Penić et al., 2020).

The intervention in this study consists of two exercise programs. It is a well-documented, safe procedure; to our knowledge, there is no previous evidence

of harm caused by its use. An emergency unblinding protocol would be implemented in specific cases. Unexpected patients with critical pain or several physical dysfunctions would require immediate medical management. Patients will receive standard care treatment for their adverse events. In these cases, an assigned investigator will record the event and proceed to contact the principal investigators.

Adherence

At the physician's appointment, patients will be potentially selected. The patient will be told what kind of treatment is usually done for this procedure. If you agree, after undergoing the procedure with PRP, the patient will be referred to the care center selected by the patient or by the doctor, not interfering with the preference of the participant. According to the center, the physical therapy treatment (Group A or B) will be carried out.

The following information will be provided in the initial physical therapy session: study's objectives, mode of progression of physical therapy interventions, the importance of continuing with the treatment prescribed by your treating physician. In addition, the following strategies will be used to ensure compliance with each visit: clinical record in the patient file, the Calendar with the next visit's dates and times, reminders via email and telephone contact at the next time of your visit.

Timeline

The study enrolment will require 12 months, including 15 days of run-in evaluation, as shown in Figure 2. The physical therapy sessions will be completed in four weeks (3 sessions per week).

Outcomes

Primary outcome measures

The primary outcome is the ultrasound tendon size measurement. The average difference in means between baseline and 6-week measurements will be estimated. Then we will control the outcomes every four months. Figures 3A and 3B show that the professionals will be using an Aplio 500 US system (Toshiba America Medical Systems, Inc, Tustin, CA, ca.medical.canon) with an 18 MHz multifrequency linear transducer to tell the IST about the LET exams.

Reducing at least 80% of tendon tear from the baseline using LP-PRP US-guided will be clinically significant.

Secondary outcome measures are: (i) pain testing using a visual analog scale will be performed at baseline and every four months. As an ordinal variable, a median will be reported for each group; (ii) the

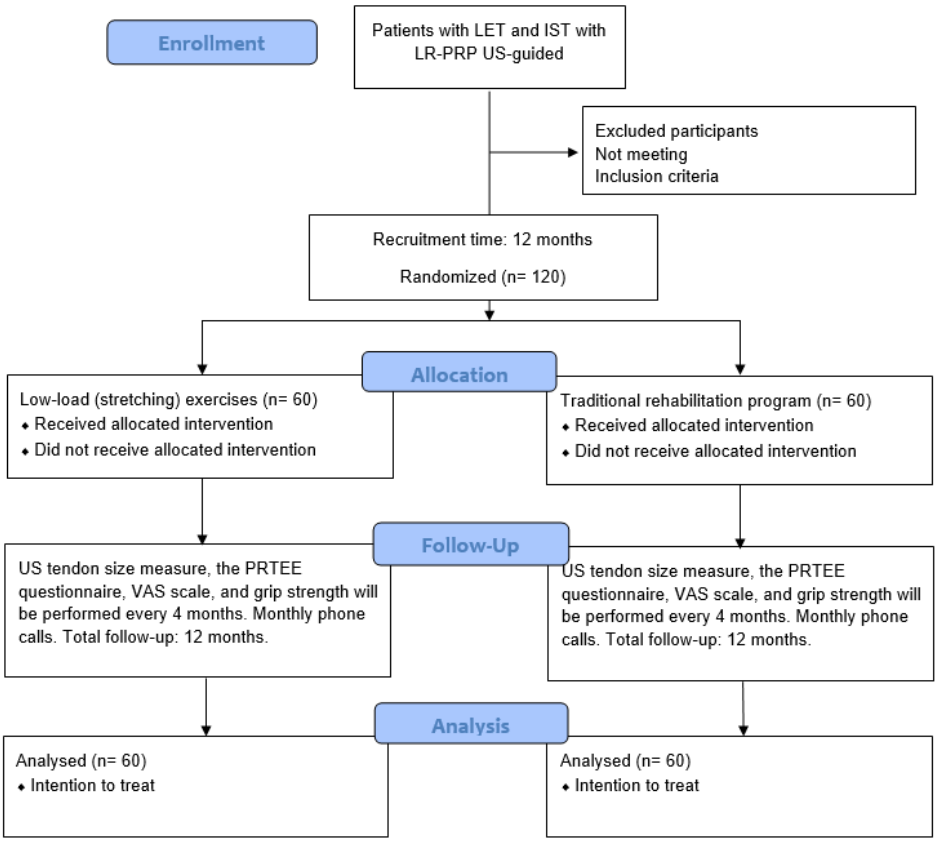

Figure 2. The timeline diagram.

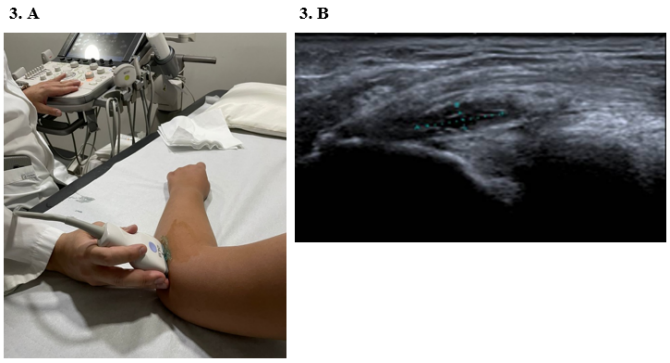

Figure 3. 3.A. Common extensor tendon ultrasound examination. **3. B**. Intrasubstance tear confirmation in the common extensor tendon of the right elbow using musculoskeletal ultrasound. Male patient with 58 years. Distance A was 7 millimeters, and distance B was 2 millimeters.

functionality will be evaluated at baseline and every four months with the PRTEE questionnaire. It is a specific instrument available for assessing the health status of patients with LET. As an ordinal variable, a median will be reported for each group; (iii) handgrip, wrist flexion, and extension strength will be performed at baseline and every four months with a dynamometer. These variables will be reported as a continuous secondary outcome for each group, and the analysis will be based on the difference in means at each time point.

Data Management

Other variables such as date, patient age, weight, height, dominance, elbow side injury, systemic diseases, symptom time, and sleep quality will also be measured. The data of interest will be entered electronically. A data matrix will be enabled in Google FORMS, where the evaluating professionals will have access to it. For more information, please visit the variables link in appendix number 2.

Data anonymization will be guaranteed by a bioinformatic professional. Using this data entry system reduces time and costs. Codifications of standardized terminologies will be established to minimize misinterpretation. The project statistician will make sure that the data collected, processed, and analyzed is of good quality.

The data will be destroyed after five years or after the termination of the study. A data user agreement will be developed establishing the protocol for sharing information with any eventual collaborators.

Data Monitoring Committee

The FDA recommends a Data and Safety Monitoring Board (DSMB) (FDA, 2021). Our study included a nurse, a statistician or clinical research expert, and a physical therapist specialist in orthopedics, independent from the investigators. The current interventions did not present any reported secondary adverse effects in the literature. However, the DSMB will periodically review cumulative data on adverse events. Based on the reported information, this committee will notify the investigators as soon as possible.

An interim analysis of the primary outcome will be performed when 50% of patients have been recruited and have completed their follow-up. The intermediate analysis will be the responsibility of a statistician blinded to the designation of the treatment. Interim analysis and supplementary data will support evaluating the safety, efficacy, and futility of being present. If the intervention does not work, the researchers may tell the therapist and participants.

Statistical analysis

For descriptive statistics purposes, all continuous numerical data such as tendon size measurement, handgrip, wrist flexion, and extension strength will be presented as means or medians with standard deviation (SD) and interquartile ranges (IQR), respectively, as measures of dispersion. Categorical data such as pain testing and functionality will be presented as proportions, frequencies, or percentages. For all primary and secondary analyses, the experimental intervention group will be compared with the control group.

Data normality will be evaluated using the Shapiro-Wilk test. For continuous outcomes, a paired t-test or Wilcoxon signed-rank test will be performed as appropriate. For categorical data, Chi-Square tests will be implemented. For subgroup analyses, regression methods will be used to compare interactions between groups. Multiple linear regression will be used for outcomes that are always the same, and multiple logistic regression will be used for outcomes that are either yes or no.

P-values will be reported with two decimal points. Our tests will be 2-tailed p-values with a significance level (alpha) of 0.05 to consider the statistical significance. All statistical analyses will be performed using the R (v 4.1.0) software package.

Missing Data

Missing data (or missing values) is the value of a variable in an observation of interest that is not stored (Kang, 2013). Techniques for handling the missing data will be implemented. Firstly, this is a well-planning study and data will be carefully collected. All statistical analyses will be carried out using the intention-to-treat approach, and missing data will be taken to be missing at random. Multiple imputation techniques will be used to address the secondary outcomes. A sensitivity analysis based on the best-case scenario will be

carried out to determine the degree of uncertainty associated with the missing data handling strategy. The results dependability will be evaluated with a per-protocol analysis.

Ethics statement

This study has been performed in keeping with the latest version of the Declaration of Helsinki, in accordance with Chilean legislation. The study was approved by the "Comité de Ética Científico Adulto del Servicio Metropolitano Oriente de la ciudad de Santiago de Chile (SSMO)". No approval number was recorded.

Discussion

This study looked at how well a low-load exercise protocol (stretching) might work compared to a traditional rehabilitation program for people with LET and IST under ultrasound-guided platelet-rich plasma infiltration.

Some strong points of our intervention were that we proposed one of the first studies in the literature that considered a detailed standardized exercise protocol applied to these particular patients. This proposal implemented a novel exercise model with 120 participants (all of whom were previously diagnosed with LET and IST under PRP US-guided infiltration). The recruitment strategy implemented in this study facilitates the expected sample size. Our medical institution is one of the biggest Latin American reference centers for sports medicine. Our selection criteria were proposed considering patients' characteristics treated at our center. We will only include LET with IST diagnosed by musculoskeletal ultrasound. This will cut down on the number of groups and make it more likely to find a significant intervention effect.

US-guided PRP infiltration has been proven safe, with few side effects described in the scientific literature (Le, Enweze, DeBaun, & Dragoo, 2018). Our low-load exercise protocol (stretching) is well tolerated even if they do not have the physical training, which will impact decreasing the number of patients refusing to participate, dropouts, or unblinding situations.

Previous published studies have analysed the effect of PRP and eccentric exercise programs in the treatment of patellar and Achilles tendinopathies with functional outcomes (De Vos et al., 2010; Droppelmann, 2021; Kaux et al., 2014; Van Ark, Van den Akker-Scheek, Meijer, & Zwerver, 2013) However, these programs vary from PRP concentration to different exercise load progression. Only a few case reports have been published using PRP versus an eccentric exercise program for patients with LET. The authors have justified using this strategy to optimize and restore their long-term function. Nonetheless, they exhibited only one 48-year-old male evaluated (Ihm, Mautner, Blazuk, & Singh, 2015).

This study has some limitations. For example, it will not be possible to control the activities of daily life or sports of each of the participants, which may cause an overload of the affected area or impact a decrease in the effectiveness of the intervention. Patients with LET present different peripheral and central neurological adaptations that cannot be evaluated and controlled, so different responses to treatment are expected. A selection bias and loss of external validity due to obtaining the participants are identified. This is because the participants are selected by convenience sampling. In addition, both the intervention group and the control group will be under the evaluation of a standardized exercise program. However, they are differentiated by the exercise load of each one and may not achieve significant differences between them. In any case, the current study will make it possible to measure the differences between the outcomes from the baseline condition of the participants to the end of the process. This will let us figure out how well the PRP plus an exercise program works, no matter the load.

The authors of this research protocol hope that the results obtained can be applied in future lines of action. Our primary interest is to find the best way to reduce the size of tendon tears, and improve the prognosis, treatment times, and economic costs, which will improve the quality of life of patients and athletes.

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Conflicts of Interest: The authors declare no conflict of interest.

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