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Systematic Review and Meta-Analysis

Photobiomodulation effects on Achilles tendon pain: a systematic review and meta-analysis of randomized clinical trials

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HIGHLIGHTS

- Studies with photobiomodulation and Achilles tendon pain have a high risk of bias.
- The included studies showed very low- to low-quality evidence.
- There is no photobiomodulation effect in Achilles tendon pain.

ABBREVIATIONS

CI	Confidence intervals
I^2	inconsistency test
PEDro	Physiotherapy Evidence Database
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
SD	Standard deviation
SMD	standardized mean difference

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BACKGROUND: Achilles tendon pain is present in tendons' non-rupture injuries usually exacerbated by mechanical loading (i.e., overuse injury). Photobiomodulation is a light therapy that may reduce pain in tendinopathy.
AIM: This systematic review and meta-analysis of randomized clinical trials tested the acute and chronic effects of photobiomodulation on Achilles tendon pain.
METHOD: Randomized clinical trials were included comparing photobiomodulation with a control group in patients with Achilles tendon pain. The search included MEDLINE (Pubmed), SCOPUS, EMBASE, Physiotherapy Evidence Database (PEDro), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), LILACS, and Science Direct databases, and manual search until November 2021. The bias's risk was assessed by the Cochrane Collaboration bias risk assessment tool and PEDro scale, while the level of evidence strength by the GRADE. Quantitative analysis through meta-analyzes was performed. The protocol was registered (PROSPERO-CRD42018091509).
RESULTS: The search yielded 3.239 papers in the seven databases. Five studies were included after screening, eliminating duplicates, and applying eligibility criteria, and three were included in the meta-analysis. The meta-analysis (n=79) showed no photobiomodulation acute and chronic effects compared with control group on Achilles tendon pain (p= 0.45, SMD: 0.28). In the qualitative analysis, three studies showed a high risk, and two studies a low risk of bias in all characteristics. GRADE analysis showed very low- to low-quality evidence of the studies.
CONCLUSION: There is no photobiomodulation effect in Achilles tendon pain. Due to the very low and low strength of evidence, new studies with better methodological quality should be conducted to improve the level of evidence.

KEYWORDS: Achilles tendon | Photobiomodulation | Low-level laser therapy | Tendinopathy | Pain | Ankle

INTRODUCTION

Achilles tendon disorders are related to overuse injuries and complete, spontaneous rupture [1]. However, the number and incidence of Achilles tendinopathy cases increased in the last decade [2,3]. Tendinopathy is a term used to indicate a non-rupture injury in the Achilles tendon that is exacerbated by mechanical loading. The Achilles tendon is often exposed to different stresses (e.g., tension, compression, and shear), and when these loads exceed the tendon's physiological capacity, the Achilles tendon is exposed to a cumulative cycle of injury with inflammation and repair. These cycles lead to swelling and pain, which characterizes tendinopathy [4].

A common symptom in patients with tendinopathy is pain [4], which changes their movement pattern. This pain and swelling in the posterior aspect of the ankle make daily-life activities difficult to be executed. The pain increases after high tendon loading conditions such as running hills, stairs, or running on toes [5]. Tendinopathy is characterized

by collagen disruption/tearing, inflammation, and tenocyte response [4,6,7,8]. An inflammatory

response in the tendon is seen when a tendon (and its blood supply) is ruptured or lacerated, with a large immune cell and tenocyte response increases protein production and tendon size. The tenocyte is primarily responsible for maintaining the extracellular matrix in response to its environment. Thus, changes in tendon load and biochemical changes will be sensed by the tendon cells and result in a cascade of responses (cell activation, proteoglycan expression and changes in collagen type) [6].

An interesting strategy for treating Achilles tendinopathy is photobiomodulation [9]. Photobiomodulation interventions involve the energy coming from monochromatic light sources that are used in a large scale with therapeutic objectives [10]. The use of photobiomodulation therapy has been growing over the years, being a low-cost therapy with low adverse effects. Preview studies investigated the phototherapy effectivity in the Achilles tendon healing in rats and observed an increase of type I collagen synthesis [11,12]. The energy absorbed by the mitochondria during light therapy stimulates ATP production and increases intracellular calcium concentration resulting in tenocytes proliferation and collagen synthesis [12].

The photobiomodulation effect on the tendinopathy process (in female aged rats with reduced type I collagen) [13] restored type I collagen levels. The phototherapy per point application also reduced inflammation and pain in activated Achilles tendinopathy [14]. Previous studies investigated the photobiomodulation's effectivity in the Achilles tendon healing in rats and observed increased type I collagen synthesis [12,15]. More recently, the use of photobiomodulation therapy for anti-inflammatory action, with local and systemic effects, is being studied. In Achilles tendinopathy, a reduction in the inflammatory process was observed after photobiomodulation [16]. Photobiomodulation was shown to acutely reduce inflammation and pain in Achilles tendinopathy patients [17]. However, another study using the World Association for Laser Therapy's parameters did not find clinical effectiveness in adding photobiomodulation to eccentric exercises for the treatment of Achilles tendinopathy [18], showing no photobiomodulation's aditional benefical effect.

Two recent systematic reviews verified the photobiomodulation effect on pain in patients with tendinopathies [19,20]. Doyle et al. [19] found five relevant studies indicating that photobiomodulation decreases pain from baseline measurements. However, from their five included studies, only two studies [21,22] indicated clinical effectiveness in pain when comparing photobiomodulation with placebo treatment. Therefore, the inconsistent findings on the photobiomodulation clinical effects to decrease tendinopathy pain may not be warranted [19]. Nevertheless, this systematic review did not perform a meta-analysis and quality of evidence evaluation. In addition, they included studies with tendinopathies at different regions of the body. Martimbianco et al. [20] showed that only two studies from four trials demonstrated positive effects of photobiomodulation on Achilles tendinopathy [17,22]. However, they did not show the studies' quality of evidence analysis.

Based on these studies' results, a new systematic review that includes only randomized clinical trials on tendinopathy pain reduction due to photobiomodulation therapy is necessary. In this direction, we wanted to know if photobiomodulation is more effective to reduce pain than placebo or other interventions (e.g., aloe gel) in Achilles tendinopathy patients. This systematic review with meta-analysis followed the GRADE recommendations of randomized clinical trials while investigating the photobiomodulation effect on Achilles tendon pain.

METHODS

The systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42018091509. The study selection, data extraction, methodological quality of the included studies, and the certainty of evidence were conducted by two independent investigators (EM and FCS). When there was disagreement between the reviewers' results, a third reviewer (ESR) was consulted to reach a consensus.

Data sources and search strategy

The studies were selected from the electronic databases MEDLINE (using Pubmed), SCOPUS, EMBASE, Physiotherapy Evidence Database (PEDro), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), LILACS, and Science Direct. The search was performed until November 2021. In addition, a manual search was done in the references of published studies on the subject. Controlled and uncontrolled descriptors were used for population, assessment, and outcome (Table 1).

Table 1. Search strategy using MESH terms on the PUBMED.

Terms for search	MESH terms used
Participants	**"Achilles Tendon"[Mesh]** OR "Achilles Tendon" OR "Tendon, Achilles" OR "Calcaneal Tendon" OR "Calcaneal Tendons" OR "Tendon, Calcaneal" OR "Tendons, Calcaneal" OR "Tendo Calcaneus" OR **"Tendon Injuries"[Mesh]** OR "Tendon Injuries" OR "Injuries, Tendon" OR "Injury, Tendon" OR "Tendon Injury" OR **"Tendinopathy"[Mesh]** OR "Tendinopathies" OR "Tendonopathy" OR "Tendonopathies" OR "Tendinosis" OR "Tendinoses" OR "Tendonosis" OR "Tendonoses" OR "Tendinitis" OR "Tendinitides" OR "Tendonitis" OR "Tendonitides" OR **"Tendons"[Mesh]** OR "Tendon" OR "Tendons, Para-Articular" OR "Para-Articular Tendon" OR "Para-Articular Tendons" OR "Tendon, Para-Articular" OR "Tendons, Para Articular" OR "Tendons, Paraarticular" OR "Paraarticular Tendon" OR "Paraarticular Tendons" OR "Tendon, Paraarticular" OR "Epotenon" OR "Epotenons" OR "Endotenon" OR "Endotenons" OR **"Rupture, Spontaneous"[Mesh]** OR "Rupture, Spontaneous" OR "Ruptures, Spontaneous" OR "Spontaneous Rupture" OR "Spontaneous Ruptures" OR **"Rupture"[Mesh]** OR "Rupture" OR "Ruptures" OR "Achilles tendon rupture"
Intervention	**"Phototherapy"[Mesh]** OR "Phototherapy" OR "Phototherapies" OR "Therapy, Photoradiation" OR "Photoradiation Therapies" OR "Therapies, Photoradiation" OR "Light Therapy" OR "Light Therapies" OR "Therapies, Light" OR "Therapy, Light" OR "Photoradiation Therapy" OR **"Low-Level Light Therapy"[Mesh]** OR "Light Therapies, Low-Level" OR "Light Therapy, Low-Level" OR "Low Level Light Therapy" OR "Low-Level Light Therapies" OR "Therapies, Low-Level Light" OR "Therapy, Low-Level Light" OR "Photobiomodulation Therapy" OR "Photobiomodulation Therapies" OR "Therapies, Photobiomodulation" OR "Therapy, Photobiomodulation" OR "LLLT" OR "Laser Therapy, Low-Level" OR "Laser Therapies, Low-Level" OR "Laser Therapy, Low Level" OR "Low-Level Laser Therapies" OR "Laser Irradiation, Low-Power" OR "Irradiation, Low-Power Laser" OR "Laser Irradiation, Low Power" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Laser Therapy, Low-Power" OR "Laser Therapies, Low-Power" OR "Laser Therapy, Low Power" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Biostimulation, Laser" OR "Laser Phototherapy" OR "Phototherapy, Laser"
Study design (Robinson and Dickersin 2002)	((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]))

Eligibility criteria

A PICOT approach was applied to formulate the research question. This

systematic review included randomized clinical trials that compared photobiomodulation versus control group in individuals with Achilles tendon disorders (e.g. acute or chronic tendinopathy) that included pain as a symptom until November 2021. In order to avoid a risk of bias for language, no restriction of language and no restriction of publication year was imposed. Systematic review studies, letters to the editor, and editorials were excluded. The inclusion criteria were: i) being a randomized controlled trial; ii) be conducted with an individual with Achilles tendon disorders; and iii) use photobiomodulation therapy by the low-level laser therapy.

Study selection

In the first phase of the selection, the reviewers assessed the titles and abstracts of the studies identified by the search strategy. All the abstracts that did not give sufficient information regarding the inclusion and exclusion criteria were selected to assess the complete article. In the second stage, the reviewers assessed the complete articles and selected the studies following the eligibility criteria. Homogeneous studies (patient characteristics, number of participants, age, and similar details of the intervention) were included in the meta-analysis.

Data extraction

A standardized worksheet was used to extract the data in the meta-analysis. Data extracted were the average value of the outcomes, the standard deviation, and the number of subjects for all outcomes. Specifically, the average pre- and post-intervention values were extracted, as well as the pre- and post-intervention standard deviation (SD) and the number of participants. These data were extracted for both the control group and the photobiomodulation group. We used the delta values - the difference between the final value (post) and the initial value (pre) - of the outcome for each group in the meta-analysis.

In addition, data were extracted to characterize the included studies. This data included the authors and year of publication, sex, and age of the participants, number of participants, characteristics of the intervention performed (total duration, weekly sessions, time of each session and total irradiated energy), as well as statistical results related to the outcome investigated and the authors' conclusion.

Data items (outcome)

Our primary outcome was pain. Other outcomes [resumption of training; return to play; functional ability; tendon thickness; tendon vascularization; PGE2 (prostaglandin E2) concentrations; morning stiffness severity; crepitation; tenderness; active ankle dorsiflexion; functionality; and tendon thickness] were exported and are presented in the results section.

Quality appraisal and risk of bias

The risk of bias was evaluated according to the PRISMA recommendation [18]. Study quality assessment included adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluators, use of intention-to-treat analysis, and description of losses and exclusions and was assessed by the Cochrane Collaboration bias risk assessment tool [24].

The PEDro scale evaluated the quality assessment of the included studies. PEDro scores of 6 points or higher were classified as "high quality", whereas studies with 5 points

or lower were classified as "low quality" [25,26]. PEDro scores were not used as inclusion/exclusion criteria but rather as a basis for best-evidence synthesis and to discuss the studies' strengths and weaknesses.

Synthesis of results

Initially, the authors and year of the studies, the mean, standard deviation, and the number of subjects were extracted. As the outcome presented the same unit of measure but was analyzed by different scales, standardized mean difference (SMD) between the means was used. The delta values (mean post-value minus the pre-value, if the groups were different at baseline) or the final values (used if the groups were equal at baseline) were used depending on the included studies' results. SMDs were categorized as small (0.59), medium (0.6 - 1.19) or large (1.20) [27]. Posteriorly, the meta-analysis was calculated using a random-effect model and effect measures for continuous outcomes. Confidence intervals (95% CI) were determined, and $p \leq 0.05$ was adopted as the significance level. The statistical heterogeneity of the effects was assessed using the inconsistency test (I^2), in which values above 25% and 50% were considered as indicative of moderate to high heterogeneity, respectively [28]. If there was moderate or high heterogeneity between the studies, sensitivity and subgroup analyzes (e.g., duration of intervention) was performed. All analyzes were performed using the program Review Manager, Version 5.3 (Cochrane Collaboration).

Summary of evidence

The quality of evidence was assessed using the GRADE approach [29]. The quality of evidence of the included studies refers to a body of studies and not to individual studies. Some factors, such as the risk of bias, inconsistency, indirectness, imprecision, and publication bias, are associated with this judgment, and they may lead to upgrading or downgrading the quality of evidence of an outcome from a group of studies. The quality of evidence can be presented in four categories: high (enough evidence in the estimate of the effect), moderate (the true effect is close to the estimate of the effect), low (the confidence of the effect is limited), and very low (little confidence of the effect estimate) [30].

RESULTS

Study selection

The search by the defined terms yielded 3.239 studies. After screening all study titles and eliminating duplicates from the different databases, 64 potentially eligible studies were identified. Following the abstract examination, 39 studies remained included. However, the full-text assessment showed that only five studies confirmed all criteria and, thus, more than twenty-four studies were excluded from further analysis. The screening of the reference lists of the included studies did not provide additional eligible studies. From these five included studies, four were included in the meta-analysis (one was excluded because it used a pharmacological cream with the intervention; Figure 1). All five studies were evaluated qualitatively.

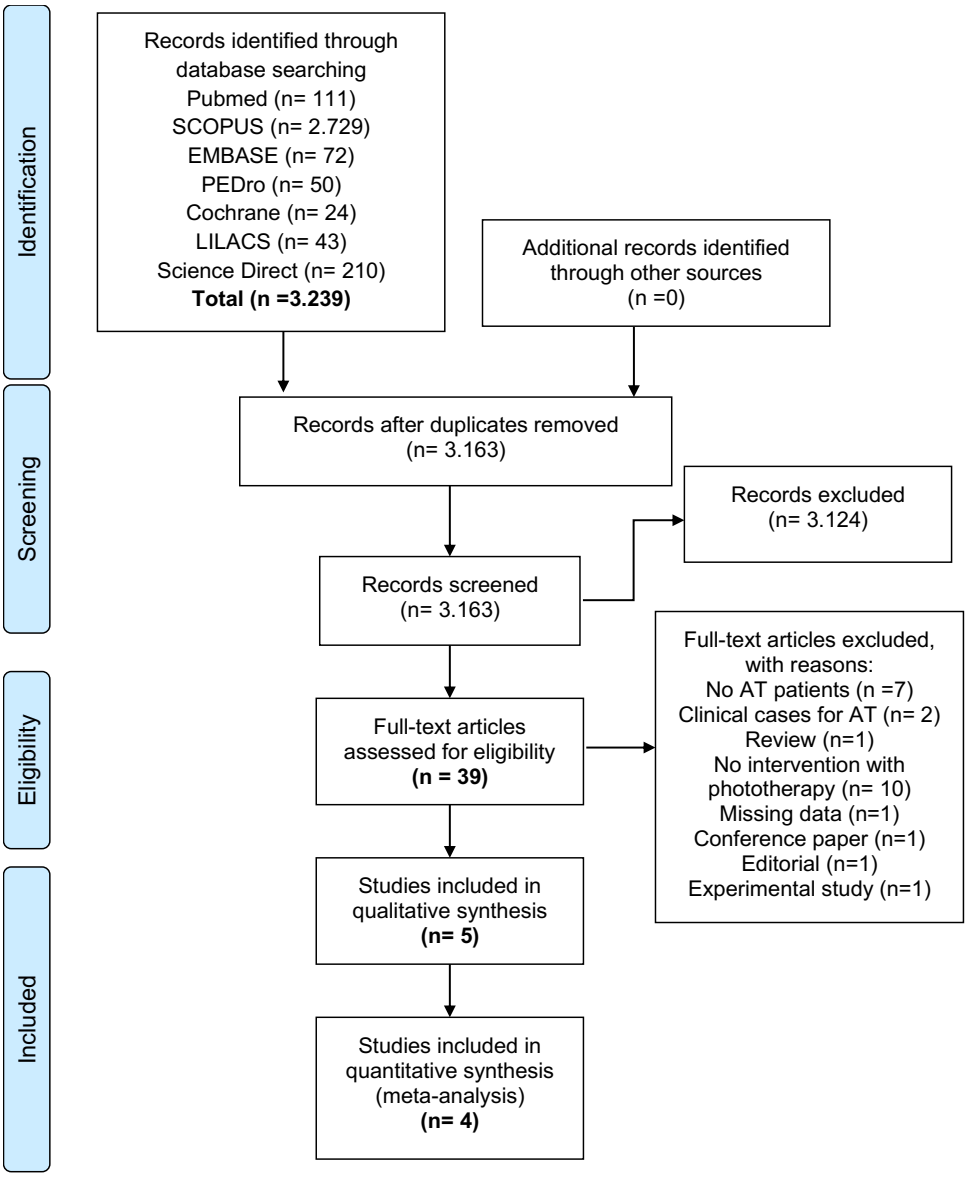

Figure 1. Flow diagram based on Moher, Liberati et al. (2009).

Study characteristics

The characteristics of the five included studies are described in Table 2 and Table 3. Table 2 shows a large variability in the intervention duration from 1 session (one day) to 12 sessions (up to eight weeks) and photobiomodulation power density (20 to 1670 mW/cm^2); however, it also presents a small variability in the light therapy wavelength (810 to 980 nm). Table 3 shows a large variability of the participants' number (7 to 80). In addition, one study applied another intervention (i.e., aloe gel) than placebo as control group [31], and three studies combined the photobiomodulation application with eccentric exercise during the intervention period [18,22,32].

Table 2. Photobiomodulation parameters.

Parameters	Ammendolia et al., (2016)	Bjordal et al., (2006)	Stergioulas et al., (2008)	Tumilty et al., (2012)	Tumilty et al., (2016)
Duration of intervention	10 sessions (daily session)	1 session	12 sessions (2x/week - first 4 weeks; 1x/week - second 4 weeks)	12 sessions (3x/week for 4 weeks)	8 sessions (2x/week for 4 weeks)
Wavelength	904 nm	904 nm	820 nm	810 nm	810 and 980 nm
Optical output	Did not present	30 mW	30 mW	100 mW	5.000 mW
Irradiation area/ spot size	Did not present	0.5 cm²	0.5 cm²	0.07 cm²	3 cm²
Power density	25 mW/cm² (pulsed mode)	20 mW/cm².	60 mW/cm²	100 mW/cm²	1.670 mW/cm²
Number of irradiation points	Did not present	3	6	6	Sweeping motion from the calcaneus to 10 cm proximal
Energy per point in each session	Did not present	1.8 J	0.9 J	3 J	150 J
Total energy per session	Did not present	5.4 J	5.4 J	18 J	450 J
Total energy delivered in treatment	Did not present	5.4 J	64.8 J	216 J	3.600 J

Table 3. Characteristics of the included studies. Y means year; LLLT: low-level laser therapy; VAS: Visual analog scale.

STUDY	DISORDER	SAMPLE	OUTCOMES	MEASUREMENT	CONTROL (CG)	RESULTS	CONCLUSION	QUALITY ASSESSMENT (PEDRO SCORE)
Ammendolia et al., (2016)	Tendinopathy (n=35)	35 elite volleyball athletes	(1) Pain intensity; (2) Resumption of training; (3) Return to play.	(1) Visual analogue scale; (2) and (3) days.	3 ml gel (aloe *barbadensis extract*) 3x/day by 10 days	(1) Pain relief in 10 days in CG; (2) LLLT group return training earlier than CG; (3) CG return to play earlier than LLLT	Healing tendinopathy in a short time, using a topical therapy based on micronutrient as a gel, that the athletes can self-administer several times a day.	Low Quality (4/10)
Bjordal et al., (2006)	Pain (n=7)	Patients recruited through primary care by doctors and physiotherapists	(1) Pain intensity; (2) Functional ability; (3) Tendon thickness; (4) Tendon vascularization; (5) PGE_2 concentrations.	(1) Pressure pain threshold in painful spot (2) distance in the single leg hop test; (3) Caliper; (4) Doppler; (5) Microdialysis.	Placebo.	(1) Non-significant decrease in the pain after the treatment; (2) Both groups showed a decrease in the single jump hop test after treatment; (3) They did not show the result. (4) No significant differences between groups were observed after treatment; (5) In LLLT group a small decrease in PGE_2 concentration was seen first one hour after treatment, and then gradually decreasing from baseline at the last time point 105 minutes after treatment. CG, PGE_2 concentrations increased gradually in the period after treatment from baseline to at the last observation.	LLLT can be used to reduce inflammatory musculoskeletal pain.	High Quality (7/10)

Stergioulas et al., (2008)	Tendinopathy (n=20)	Patients self-referred or referred by their physician for treatment of their Achilles tendinopathy.	(1) Pain during activity; (2) Morning stiffness severity; (3) Crepitation; (4) Tenderness (5) Active ankle dorsiflexion.	(1) 100 mm VAS; (2) 100 mm VAS; (3) 100 mm VAS; (4) 40 mm VAS; (5) Goniometry.	Placebo.	(1) Pain was significantly lower in the LLLT group than in CG; (2), (3), (4) and (5) were significantly better (P < .05) in the LLLT group than in the CG.	LLLT seems to be a safe and effective method for more rapid recovery when combined with an eccentric exercise regimen.	High Quality (7/10)
Tumilty et al., (2012)	Tendinopathy (n=40)	Diagnosis of Achilles tendinopathy affecting the midportion of the tendon.	(1) Functionality; (2) Pain.	(1) VISA-A questionnaire (2) Numeric Pain Rating Scale (score between 0 and 10)	Placebo	(1) favored to the CG; (2) LLLT group displayed inferior numeric pain scores initially but failed to demonstrate any superior gains that may have resulted from the adjunct laser treatment at all other assessment points.	Clinical effectiveness of adding LLLT to eccentric exercises for the treatment of Achilles' tendinopathy has not been demonstrated.	High Quality (10/10)
Tumilty et al., (2016)	Tendinopathy (n=80)	Patients with a diagnosis of Achilles tendinopathy greater than 3 months.	(1) Functionality; (2) Pain; (3) Tendon thickness.	(1) VISA-A questionnaire (2) Numeric Pain Rating Scale (score between 0 and 10) (3) Ultrasound	Placebo.	(1) all groups had improved their VISA-A (2) Pain decreased for all groups. (3) Tendon thickness reduced significantly over the course of the intervention, but there was no significant difference in these changes between groups at 12 weeks.	Photobiomodulation using the parameters stated above as adjunct to eccentric exercise can induce added benefit at 12 weeks	High Quality (9/10)

Analysis of the risk of bias and methodological quality

The bias risk analysis results are presented in Figure 2. The analysis was made considering the five included studies. In Figure 2, we have six data points because the Tumilty et al. [32] was duplicated due to the two different groups' comparisons of photobiomodulation versus placebo. Bjordal et al. [17], Ammendolia et al. [31], and Stergioulas et al. [22] had an unclear risk of bias for their reporting not being registered on clinical trials. Bjordal et al. [17] and Ammendolia et al. [31] had a high risk of bias for incomplete outcome data because they did not show an intend-to-treat analysis. Tumilty et al. [18] and Tumilty et al. [32] had a low risk of bias for all analyzed biases, and therefore they were considered the best methodological studies.

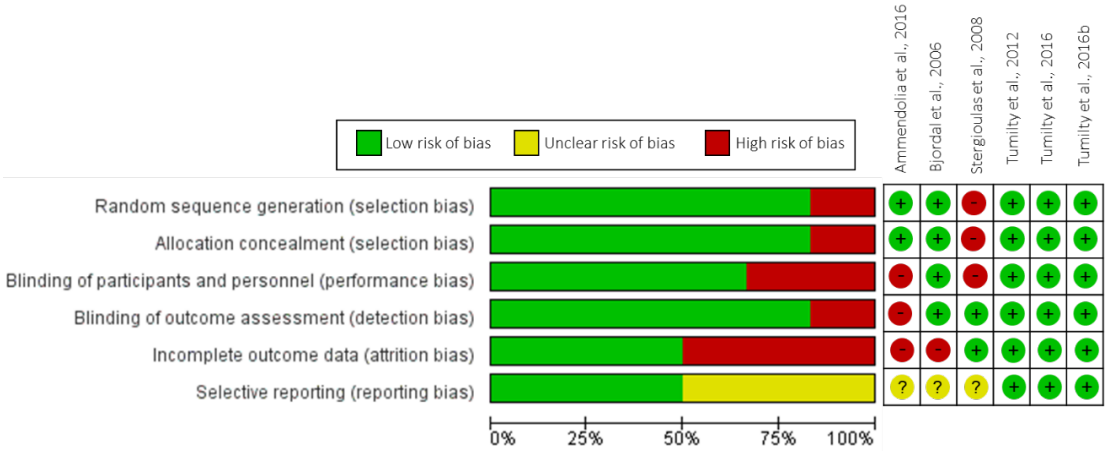

Figure 2. Risk of bias of the included studies.

PEDro scale analyses of the included studies are presented in Table 4. Ammendolia et al. [31] was the only study with low quality (4/10), whereas the other included studies were classified as high quality by the PEDro scale score [25,26], with the highest score being obtained by Tumilty et al. 18 with 10/10 points. Only criteria 1, 2, and 10 of the PEDro scale were contemplated in all studies. However, the GRADE approach presented a very low quality for the four studies with pain as the outcome, including those that analyzed pain up to 8 weeks (Table 5). In addition, three studies that analyzed pain up to 4 weeks presented a low quality due to the risk of bias, inconsistent results, and imprecision (Table 5).

Table 4. PEDro scale score of the included studies. N: No; Y: Yes.

Questions \ Studies	Ammendolia et al., (2016)	Bjordal et al., (2006)	Stergioulas et al., (2008)	Tumilty et al., (2012)	Tumilty et al., (2016)
1. Eligibility criteria were specified	Y	Y	Y	Y	Y
2. Subjects were randomly allocated to groups	Y	Y	Y	Y	Y
3. Allocation was concealed	Y	Y	N	Y	Y
4. The groups were similar at baseline	N	N	Y	Y	Y
5. There was blinding of all subjects	N	Y	Y	Y	Y
6. There was blinding of all therapists who administered the therapy	N	Y	N	Y	N
7. There was blinding of all assessors who measured at least one key outcome	N	Y	Y	Y	Y
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Y	N	N	Y	Y
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"	N	N	Y	Y	Y
10. The results of between-group statistical comparisons are reported for at least one key outcome	Y	Y	Y	Y	Y
11. The study provides both point measures and measures of variability for at least one key outcome	N	Y	Y	Y	Y
Total	**4/10**	**7/10**	**7/10**	**10/10**	**9/10**

Table 5. Quality of evidence using the GRADE approach.

			Certainty assessment				N			
Outcome	**N**	**Type**	**ROB**	**Inconsistency**	**Indirectness**	**Imprecision**	**PBMT**	**Placebo**	**Absolute (95% CI)**	**Certainty**
Pain	**4**	RCT	serious[a]	very serious[b]	not serious	very serious[c]	124	124	0.08 [-0.28, 0.44]	VERY LOW
Pain (up to 4 weeks)	**3**	RCT	not serious	not serious	not serious	very serious[c]	52	52	0.23 [-0.20, 0.66]	LOW
Pain (up to 8 weeks)	**4**	RCT	serious[a]	very serious[b]	not serious	very serious[c]	72	72	-0.03 [-0.60, 0.54]	VERY LOW

RCT: Randomized clinical trial; ROB: Risk of Bias; a: one study with limitation in design; b: moderate heterogeneity; c: large confidence interval; PBMT: photobiomodulation.

The meta-analysis with 79 patients with Achilles tendon pain showed no photobiomodulation effect compared with the control group (p= 0.45, SMD: 0.28, CI: -0.45 – 1.01). However, as the heterogeneity was very high (I^2=78%), we conducted a subgroup analysis for the intervention duration and a sensitivity analysis without a study that had a high risk of bias (Figure 2), and therefore the heterogeneity decreased (I^2=19%). Even with the sensitivity analyzes, the result remained the same, with no photobiomodulation effect

for Achilles tendon pain (p=0.30, SMD: 0.23, CI: -0.2 – 0.66).

DISCUSSION

This systematic review with meta-analysis summarizes the existent evidence on the photobiomodulation effects on Achilles tendon pain. The aim was to answer if photobiomodulation therapy is more effective in reducing Achilles tendon pain compared with a control group. Our main results showed no photobiomodulation effect in patients with Achilles tendon pain. In addition, we found a large variability in the intervention durations and photobiomodulation parameters, making between-interventions comparisons difficult.

A recent review of the photobiomodulation effect on tendinopathies [19] showed a beneficial effect for the tendinopathies' treatment. However, although they showed a significant decrease in pain from baseline, its use is no better than placebo or traditional treatments such as ultrasound, moist heat packs, electrical stimulation, or therapeutic exercise to reduce pain associated with tendinopathy [19].

It is important to highlight that tendon pain is related to function, and tendinopathy decreases the ability of the muscle to repeatedly generate appropriate force that enables the tendon to store and release energy for movement. However, these changes in muscle-tendon function also occur in the presence of structural pathology, independent of pain [6]. One study [22] showed that pain decreased in the photobiomodulation group compared with the placebo group for all evaluation moments (fourth, eighth, and twentieth week). However, these authors used photobiomodulation combined with eccentric exercise, which also present clinical benefits to patients with tendinopathy due to the high mechanical load that stimulates matrix remodeling (degradation and synthesis) [6], modulating tendon structure and improving function [33].

A recent systematic review [20] showed that three of the included studies combined photobiomodulation with eccentric exercise, and just one of them demonstrated pain relief. Therefore, the eccentric exercise effect seems to be more important for the resolution of tendinopathy than photobiomodulation alone. In addition, they assessed the same level of evidence by GRADE found by us, which was classified as very low to low, suggesting that better quality studies are needed to clarify this point.

We observed that the included studies had some methodological limitations (table 4 and figure 2), and only one study had an excellent methodological procedure and low risk of bias [18]. This study aimed to determine the most clinically effective loading regimen for Achilles tendinopathy and determine if any extra benefit could be gained from adding photobiomodulation combined with eccentric exercises. The authors found that the pain decreased for all patients after the exercise intervention. Adding photobiomodulation to the treatment provided additional gains, but only to the group receiving the combination of photobiomodulation with two eccentric exercise sessions per week. Thus, it seems that the combined effect of exercise, especially eccentric exercises, with the photobiomodulation therapy is more important than this light therapy alone. However, Martin et al. [34] reached the conclusion of not recommending the use of photobiomodulation intervention on Achilles tendinopathy.

One study included in our review suggested that the use of photobiomodulation and the use of a gel-based on aloe *barbadensis* extract in volleyball athletes with

tendinopathy should reduce the pain [31]. They showed that the control group (aloe gel) had pain relief in 10 days and returned to play earlier than the photobiomodulation group. However, this study was considered with a high risk of bias and the worst score on the PEDro scale (4/10). For the authors, it is because the gel used contained micronutrients, including: extract of Arnica montana (anti-inflammatory), extract of Harpagophytum procumbens (inhibition of induction of the expression of a gene pro-inflammatory) and tocopherol (anti-inflammatory).

Information about photobiomodulation parameters used for the interventions were not standardized and/or were poorly described, with incomplete information, making the analysis and comparison of the results between studies difficult. The information of these parameters is very important for the clinical decision making of clinicians [35]. For example, the recommendation for the photobiomodulation treatment irradiation frequency is targeted at ~65 or ~170 J/cm^2 by the end of the treatment [19]. Photobiomodulation would reduce pain in tendinopathy if a proper treatment procedure (including exposure at the skin directly overlaying the injured tendon daily or every second day for at least 2 to 4 weeks) and the location-specific dose is used (power density and dose within a suggested optimal range) [35].

Strength and limitations

We used a systematic approach with two independent reviewers processing the articles for eligibility. In addition, a comprehensive search of several databases following the recommendations proposed by the Cochrane Back Review Group, and no language limitations were set to avoid missing relevant articles. Furthermore, the risk of bias of the included studies was assessed using PEDRO and Cochrane scale, meta-analysis, and the quality of evidence was assessed using the GRADE recommendations. Furthermore, we registered the review protocol before starting the research, ensuring the transparency of the review process as suggested by the PRISMA statement.

A limitation of this review is the low number of articles identified on the topic that met the eligibility criteria stipulated for the present study and the limited number of articles selected. Moreover, the studies used very heterogeneous protocols and instruments for the analyses of the outcomes. For example, the discrepancy in sample sizes between the studies; heterogeneity of the population; different parameters of photobiomodulation used; the low and moderate items at risk of bias of the studies were some of the limitations found.

Further attention should be taken in reporting photobiomodulation therapy parameters and used devices. These parameters should be shown in detail, in order to provide accurate information for the reader and allowing the study replication by other scientists [36].

Finally, more research is needed in this area with greater sample size, better methodological design, and detailed photobiomodulation therapy parameters to increase the quality of evidence and allow a better conclusion regarding the photobiomodulation effects on pain in patients with Achilles tendinopathy.

CONCLUSION

There is no effect of the photobiomodulation application alone only in Achilles tendon pain in patients with Achilles tendinopathy. Few randomized clinical trials analyzed the photobiomodulation effects on Achilles tendon pain. Photobiomodulation seems do not to provide additional gains to the eccentric exercise program.

Despite the detailed analysis of the individual studies, results must be viewed with caution due to the very low- to low-quality evidence of the reviewed studies. Therefore, additional high-quality studies are needed to shed light on the photobiomodulation effects in Achilles tendon pain, thereby providing evidence-based scientific support for health professionals' clinical practice.

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