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Complete List of Authors:	Naterstad, Ingvill; University of Bergen, Department of Global Public Health and Primary Care Joensen, Jon; University of Bergen, Department of Global Public Health and Primary Care Bjordal, Jan; University of Bergen, Department of Global Public Health and Primary Care Couppe, C; Bispebjerg Hospital, Institute of Sports Medicine Copenhagen Lopes-Martins, Rodrigo; Universidade do Vale do Paraíba, Instituto de Pesquisa & Desenvolvimento Stausholm, Martin; University of Bergen, Department of Global Public Health and Primary Care
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Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

Ingvill Fjell Naterstad[1], Jon Joensen[1], Jan Magnus Bjordal[1], Christian Couppé[2,3], Rodrigo Alvaro Brandão Lopes-Martins[4], Martin Bjørn Stausholm[1]

[1]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[2]Institute of Sports Medicine Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark
[3]Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[4]Post-Gradute Program in Pharmacology, Faculty of Medical Sciences, State University of Campinas, Sao Paolo, Brazil

Correspondence to: Ingvill Fjell Naterstad naterstad@gmail.com

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Abstract

Objectives We investigated the effectiveness of low-level laser therapy (LLLT) in lower extremity tendinopathy and plantar fasciitis on patient-reported pain and disability.

Design Systematic review and meta-analysis.

Data sources Eligible articles in any language were identified through PubMed, Embase and Physiotherapy Evidence Database (PEDro) on the 20th August 2020, references, citations and experts.

Eligibility criteria for selection of studies Only randomised controlled trials involving participants with lower extremity tendinopathy or plantar fasciitis treated with LLLT were included.

Data extraction and synthesis Random effects meta-analyses with dose subgroups based on the World Association for Laser Therapy (WALT) recommendations were conducted. Risk-of-bias was assessed with the PEDro scale.

Results LLLT was compared with placebo (10 trials), other interventions (5 trials) and as an add-on intervention (3 trials). The study quality was moderate-high.

Overall, pain was significantly reduced by LLLT at completed therapy (13.15 mm Visual Analogue Scale (VAS; 95% CI: 7.83-18.48)) and 4-12 weeks later (12.56 mm VAS (95% CI: 5.69-19.42)). Overall, disability was significantly reduced by LLLT at completed therapy (Standardised Mean Difference (SMD) = 0.39 (95% CI: 0.09-0.7) and 4-9 weeks later (SMD = 0.32 (95% CI: 0.05-0.59)). Compared with placebo-control, the recommended doses significantly reduced pain at completed therapy (14.98 VAS mm (95% CI: 3.74-26.22)) and 4-8 weeks later (14.00 mm VAS (95% CI: 2.81-25.19)). The recommended doses significantly reduced pain as an add-on to exercise therapy versus exercise therapy alone at completed therapy (18.15 mm VAS (95% CI: 10.55-25.76)) and 4-9 weeks later (15.90 mm VAS (95% CI: 2.3-29.51)). No adverse events were reported.

Conclusion LLLT reduces pain in lower extremity tendinopathy and plantar fasciitis compared with placebo, other treatments and as a supplement to exercise therapy. LLLT reduces disability to a small extent in the patients. Adhering to the WALT recommendations is advised.

PROSPERO registration number CRD42017077511

Keywords Phototherapy; Laser therapy; Tendinopathy; Plantar Fasciitis; Systematic review; Meta-analysis

Strengths and limitations of this study

- ► This review was performed in conformance with a prospective published protocol, which included a plan for subgrouping the trials by laser dose.
- ► There were no language restrictions; two (11%) of the included trials were reported in non-English language.
- ► The review includes results from an unpublished trial.
- ► The review features meta-analyses with direct comparisons between low-level laser therapy and placebo, other interventions and no intervention.
- ► Only one reviewer extracted data from the included trials, but the extracted data was checked for correctness by another reviewer.

INTRODUCTION

Tendinopathy and plantar fasciitis are common disorders resulting in substantial pain and loss of function in the lower extremity, and both disorders are especially prevalent in athletic and non-athletic populations.[1-3] The aetiology of tendinopathy and plantar fasciitis is multifactorial, and not fully understood. Risk factors for tendinopathy include overuse, acute trauma, ageing and genetic predisposition[4 5], while prolonged standing and jumping, reduced ankle dorsiflexion and obesity are known risk factors for plantar fasciitis.[6-9] Disorganised and degenerating collagen fibres, increased numbers of fibroblasts, altered composition of extracellular matrix proteins, formation of new vessels and rounding of tendon cells can be found in both tendinopathy and plantar fasciitis.[10 11]

Conservative treatment of lower extremity tendinopathy and plantar fasciitis includes an array of modalities and approaches. The effect of exercise therapy in tendinopathy is well-established, and any exercise type is preferential to wait-and-see in the earlier stages of tendinopathy.[12] However, a superiority of exercise therapy compared with other interventions has not been demonstrated. The use of non-steroidal anti-inflammatory drugs (NSAIDs) are frequently recommended in the early stages of tendinopathy and plantar fasciitis.[13-15] However, there is a lack of placebo-controlled trials investigating the effectiveness of NSAIDs in lower extremity tendinopathies.[16-20] Moreover, NSAIDs have well known and potentially fatal side-effects, most importantly severe cardiovascular events and gastrointestinal toxicity.[21] Low-level laser therapy (LLLT), also known as photobiomodulation therapy, is a quickly administered non-invasive intervention option free from negative side-effects. LLLT is an athermic photochemical modality, where red or near-infrared light is used to stimulate tissue healing, reduce pain and inflammation.[22-25] The working mechanisms of LLLT are partly established. There is evidence that LLLT increases adenosine triphosphate production[26], modulates the reactive oxygen species and the induction of transcription factors.[27-30] Besides, it has been demonstrated that LLLT inhibits cyclooxygenase-2 gene expression and prostaglandin E2 production in tendons[31 32], as well as inhibition of matrix metalloproteinase activity.[32 33] Furthermore, under application of LLLT, macrophages are more likely to act as phagocytes.[34]

There are heterogeneous results from clinical trials of LLLT in tendinopathies, and this may or may not be explained by a dose-response relationship.[35-37] Variation in LLLT parameters, such as wavelength, power density, pulse structure, application method and timing may affect the treatment outcome. Additionally, several in vivo and in vitro trials have demonstrated that when the LLLT dose is increased beyond a certain level, the response diminishes.[38-41] In a recent review by our research group regarding the effectiveness of LLLT in knee osteoarthritis, a significant dose-response relationship was discovered when the included trials were subgrouped using the World

Association for Laser Therapy (WALT) treatment recommendations.[42] Several recent systematic reviews have either solely focused on LLLT or included the modality as one of several conservative treatments in Achilles tendinopathy or plantar fasciitis.[12 43-48] Unfortunately, these reviews have one or more substantial limitations, such as a lack of a dose-response analysis[12], a lack of inclusion of trials reported in non-English languages[43-47], or the faulty use of a fixed effects meta-analysis model in the presence of highly heterogeneous studies[48].

Thus, the potential benefits of managing pain and disability associated with lower limb tendinopathy and plantar fasciitis have been investigated using LLLT but are still somewhat inconclusive. Further explorations into the clinical effectiveness of LLLT are warranted, and the objective of the current review were hence to estimate the effectiveness of LLLT in tendinopathy and plantar fasciitis on patient-reported pain and disability with a dose-response analysis.

METHODS

This review adheres to a prospectively registered PROSPERO protocol and is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009.[49]

Literature search and selection of studies

We included randomised clinical trials in which the effectiveness of LLLT in tendon disorders of the lower extremity or plantar fasciitis was compared with sham (placebo) LLLT, other interventions or no intervention, in terms of self-reported pain and/or disability. There were no restrictions regarding publication date and language.

An updated search of the databases PubMed, Embase and Physiotherapy Evidence Database (PEDro) was completed on the 20th August 2020. Furthermore, references from relevant systematic reviews[44 46 48 50 51] and all the included trials were screened, and experts in the field were asked to provide additional published and unpublished trials. Abstracts were not included. The full electronic search strategy is included in the supplementary material.

Two independent reviewers (IFN and MBS) read the titles and abstracts of the publications identified by the search. Any article judged potentially eligible by a reviewer was retrieved in full text. The same two reviewers evaluated the full texts of all the potentially eligible articles and made a careful decision to include or exclude each article, with close attention to the eligibility criteria. Any article not fulfilling the eligibility criteria was excluded and had its details listed with reason for exclusion (supplementary material). Selection disagreements were resolved by discussion to consensus with the option of a third person's (JJ) final decision if necessary.

Risk-of-bias analysis

Two reviewers (IFN and MBS) independently assessed the risk-of-bias of the included trials with the 0-10 points PEDro scale.[52] This was done on outcome level, and since the outcomes of interest are patient-assessed pain and disability, the participants were considered the assessors. Therefore, the assessors can only be blinded in placebo-controlled trials. When risk of bias disagreements could not be resolved by discussion, a third reviewer (JJ) made the final consensus-based decision. The trials were labelled as being of 'high', 'moderate' or 'poor' methodological quality if they had a total PEDro score of ≥ 7, 5-6 and ≤ 4, respectively.[53] Risk of publication bias was assessed with a funnel plot.

Data-extraction and meta-analysis

Extraction of the following information was mandatory: number of participants allocated to laser and control groups, participant characteristics, type and duration of interventions, laser-specific

application information (including location of application, wavelength, energy density per treated spot, number of spots treated, mean power density per treated spot, treatment time per spot, treated area and total number of laser sessions and laser sessions per week), selected outcome measurement scales for data-extraction, time-points of assessments, effect estimates and adverse events.

The data collection was handled in a two-person procedure by IFN and MBS. Initially, one reviewer entered all the data in Excel sheets and then another reviewer checked the extracted data for correctness. If data-extraction disagreements could not be resolved by discussion, a third reviewer (JMB) made the final consensus-based decision.

All meta-analyses were conducted using random effects models, weighting the individual trial results relatively even when statistical heterogeneity is present.

Pain results were synthesised using the Mean Difference (MD) method as this method allows for change and final scores to be combined.[54] Pain scores reported on the Visual Analogue Scale (VAS) and on the Numeric Rating Scale highly correlates[55] and were thus considered the same. Self-reported disability results were synthesised with the Standardised Mean Difference (SMD) method using change scores solely.[54] According to Cohen, a SMD of 0.2, 0.5 and 0.8 can be considered small, moderate and large, respectively.[54]

Heterogeneity was measured using I^2-statistics (inconsistency).[56] An inconsistency level of 25%, 50% and 75% would be considered low, moderate and high, respectively.[57] Standard deviations (SD) for meta-analysis were extracted or estimated from other variance data in the following prioritised order: SD, standard error, 95 % confidence interval, p-value, interquartile range, median of correlations, visually from graph, correlation of 0.6 or mean of SDs from similar trials.

Trials were subgrouped by laser dose using the World Association of Laser Therapy (WALT) treatment recommendations[58 59], as specified in the a priori protocol. WALT recommends irradiating minimum of 2-3 points on the tendon or fascia. In Achilles and patellar tendinopathy, the recommended dose with 904 nanometer (nm) wavelength laser is minimum 2 Joules per point. Utilizing 780-860 nm wavelength laser, the minimum dose is 4 Joules per point. In plantar fasciitis, the recommended minimum dose is 2 Joules per point with a 904 nm laser or 4 Joules per point with 780-860 nm laser. We subgrouped the trials as recommended dose and non-recommended laser dose. If the trial reports lacked sufficient dose parameters to be identified as recommended or non-recommended dose, they were subgrouped as unknown dose.

Two time-points of assessment were selected for analysis, that is, immediately after the end of LLLT and last time-point of assessment 2-14 weeks after completed LLLT (follow-up).

IFN and MBS performed the meta-analyses, using Excel 2016 (Microsoft) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualization or carrying out of this research.

RESULTS

A total of 870 publications were identified in the search, of which 18 trials (N = 784) were included in review and meta-analysis (Figure 1 and Table 1). LLLT was applied to participants with patellar tendinopathy in 2 trials, Achilles tendinopathy in 5 trials, and plantar fasciitis in 11 trials. LLLT was compared with placebo (10 trials), other interventions (5 trials) and as an adjunct intervention (3 trials). Two trials were reported in non-English language, and one trial was unpublished. The excluded articles were listed with reasons for omission (supplementary material). The mean age of the participants was 43.6 (minimum <18, maximum 54.5, data from 14 trials), and the mean

baseline pain intensity was 64.2 mm on the VAS (minimum 19.3 mm, maximum 85 mm, data from 18 trials). No adverse events were reported by any of the trial authors. None of the trial authors declared that they had received funding from the laser industry.

Figure 1 Flow chart illustrating the trial identification process
PEDro, Physiotherapy Evidence Database.

Table 1 Characteristics of the included trials

First author, year	Participants at baseline (intervention)*	Participants at baseline (control)*	Intervention versus control	Outcome and time of reassessment after baseline (time used for analysis in bold)
Patellar tendinopathy				
Liu 2014[60], LLLT versus ET	N: 7 Age years: ≥ 18, ≤ 23 VAS Pain mm: 67.86	N: 7 Age years: ≥ 18, ≤ 23 VAS Pain mm: 65.71	4 weeks of LLLT versus 4 weeks of eccentric ET	Pain: VAS Disability: Modified-VISA Reassessment: **4** weeks
Liu 2014[60], LLLT+ET versus ET	N: 7 Age years: ≥ 18, ≤ 23 VAS Pain mm: 67.86	N: 7 Age years: ≥ 18, ≤ 23 VAS Pain mm: 65.71	4 weeks of LLLT and eccentric exercise therapy versus 4 weeks of eccentric ET	Pain: VAS Disability: Modified-VISA Reassessment: **4** weeks
Stergioulas 2003[61]	N: 23 Age years: 29.2 VAS Pain mm: 81.7	N: 21 Age years: 29.8 VAS Pain mm: 75.9	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS Disability: Functional Index Questionnaire Reassessment: **2** and **6** weeks
Achilles tendinopathy				
Darre 1994[62]	N: 46 Age years: ≥ 18 VAS Pain mm: 58.5	N: 43 Age years: ≥ 18 VAS Pain mm: 72	2.4 weeks of LLLT versus 2.4 weeks of sham LLLT	Pain: VAS Disability: - Reassessment: **2.4** weeks
Naterstad[63] (**unpublished**)	N: 20 Age years: 45.4 VAS Pain mm: 52.9	N: 21 Age years: 45.8 VAS Pain mm: 53.8	4 weeks of LLLT and cryotherapy and 12 weeks of eccentric and concentric ET versus 4 weeks of sham LLLT and cryotherapy and 2 weeks of eccentric and concentric ET	Pain: THIP VAS most painful activity Disability: THIP VAS ADL Reassessment: **4** and **12** weeks
Stergioulas 2008[64]	N: 20 Age years: 30.1 VAS Pain mm: 79.8	N: 20 Age years: 28.8 VAS Pain mm: 81.8	8 weeks of LLLT and eccentric ET versus 8 weeks of sham LLLT and eccentric ET	Pain: VAS during activity Disability: - Reassessment: 4, **8** and **12** weeks
Tumilty 2008[65]	N: 10 Age years: 41.4 VAS Pain mm: 47.8	N: 10 Age years: 42.5 VAS Pain mm: 39	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: VAS in morning Disability: - Reassessment: **4** and **12** weeks
Tumilty 2012[66]	N: 20 Age years: 45.6 NRS Pain mm: 21.1	N: 20 Age years: 46.5 NRS Pain mm: 19.3	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: NRS Disability: - Reassessment: **4**, **12** and 52 weeks
Plantar fasciitis				
Basford 1998[67]	N: 16 Age years: 42.5 VAS Pain mm: 46.6	N: 15 Age years: 42 VAS Pain mm: 57.9	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: Pain when walking in morning Disability: Limping in morning Reassessment: 2, **4** and **8** weeks
Cinar 2017[68]	N: 29 Age years: 46.59 VAS Pain mm: 61.3	N: 22 Age years: 44.18 VAS Pain mm: 54.9	3 weeks of LLLT and stretching versus 3 weeks of stretching	Pain: VAS Disability: AOFAS-F activity limitations Reassessment: **3** and **12** weeks
Cinar 2018[69]	N: 24 Age years: 46.5	N: 17 Age years: 44 NRS Pain mm: 62	3 weeks of LLLT and 12 weeks of stretching versus 12 weeks of stretching	Pain: NRS Disability: - Reassessment: **3** and **12** weeks

	NRS Pain mm: 63			
Cinar 2018[69], ESWT	N: 24 Age years: 46.5 NRS Pain mm: 63	N: 25 Age years: 45.4 NRS Pain mm: 67	3 weeks of LLLT and 12 weeks of stretching versus 3 weeks of ESWT (2000 mJ/mm^2, session once per week) and 12 weeks of stretching	Pain: NRS Disability: - Reassessment: **3** and **12** weeks
Elsehrawy 2018[70]	N: 23 Age years: 46.4 VAS pain: 85	N:23 Age years: 46 VAS pain: 82	3 weeks of LLLT versus 2 weeks of ESWT (2050 shocks/min, 10 Hz, 2.5 bars once per week)	Pain: VAS Disability: FFI disability subscale Reassessment: **4** weeks
Kiritsi 2010[71]	N: 15 Age years: 41 VAS Pain mm: 67	N: 15 Age years: 41 VAS Pain mm: 67	6 weeks of LLLT versus 6 weeks of sham LLLT	Pain: ADL VAS Disability: - Reassessment: **6** weeks
Koteeswaran 2020[72]	N: 15 Age years: 30-60 NRS Pain: 74.7	N: 15 Age years: 30-60 NRS Pain: 72.7	2 weeks of LLLT and stretching versus 2 weeks of TUS and stretching	Pain: NRS Disability: FAAM Reassessment: **2** weeks
Lamba 2013[73]	N: 40 Age years: 40.9 VAS Pain mm: 57.5	N: 40 Age years: 40.4 VAS Pain mm: 62	4 weeks of LLLT and stretching versus 4 weeks of sham LLLT and stretching	Pain: VAS Disability: - Reassessment: 1,2, 3 and **4** weeks
Macias 2015[74]	N: 37 Age years: ≥ 18 VAS Pain mm: 69.1	N: 32 Age years: ≥ 18 VAS Pain mm: 67.6	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: VAS heel pain Disability: FFI disability subscale **8** weeks Reassessment: 1, 2, **3**, 6 and **8** weeks
Sanmak 2019[75]	N: 17 Age years: 53 VAS Pain mm: 70	N: 17 Age years: 49 VAS Pain mm: 80	4 weeks of LLLT versus 3 weeks of ESWT (2 bar with 2,000 shocks/min at 10 Hz once per week)	Pain: VAS Reassessment: **4** and **8** weeks
Ulusoy 2017[76], TUS	N: 20 Age years: 53.4 VAS Pain mm: 68.7	N: 20 Age years: 50.95 VAS Pain mm: 66.6	3 weeks of LLLT versus 3 weeks of TUS (1 mHz; 2 W/cm2)	Pain: VAS in morning Disability: - Reassessment: **7** weeks
Ulusoy 2017[76], ESWT	N: 20 Age years: 53.4 VAS Pain mm: 68.7	N: 20 Age years: 54.45 VAS Pain mm: 66	3 weeks of LLLT versus 3 weeks of ESWT (2.5 bar with 2,000 shocks/min at 10 Hz three times per week)	Pain: VAS in morning Disability: - Reassessment: **7** weeks
Yüzer 2006[77]	N: 24 Age years: 49.58 VAS Pain mm: 80	N: 30 Age years: 51.53 VAS Pain mm: 76	1.4 weeks of LLLT versus steroid injection	Pain: VAS Disability: - Reassessment: **5.4**, **13.4** and 25.4 weeks

*Numbers are means, unless otherwise stated.
ADL, activity of daily living; AOFAS-F, American Orthopedic Foot and Ankle Score Function; ESWT, Extracorporeal Shockwave Therapy; ET, exercise therapy; FAAM, Foot and ankle ability measurement questionnaire; FFI, Foot Function Index; LLLT, Low-Level Laser Therapy; NRS, Numeric Rating Scale; THIP, Tendinopathy Health Impact Profile; TUS, therapeutic ultrasound; VAS, Visual Analogue Scale.

LLLT was compared with placebo LLLT in 10 trials[61-63 65-67 71 73 74 78], and exercise therapy or stretching exercises was applied as a co-intervention in five of these trials. LLLT was compared with exercise therapy or stretching exercises in three trials.[60 68 69] A comparison between LLLT and Extracorporeal Shockwave Therapy (ESWT) in plantar fasciitis was performed in four trials.[69 70 75 76] LLLT was compared to therapeutic ultrasound in two trials[72 76], and LLLT was compared to steroid injection in one trial[77]. Recommended laser doses were applied in at least 11 trials[60-65 68 69 71 73 76] and a non-recommended dose was used in at least one trial.[66] We were unable to categorise the laser doses in the remaining six trials[67 70 72 74 75 77] due to inadequately or missing descriptions of laser parameters (Table 2).

Table 2 LLLT characteristics of the included trials

First author, year	Wave-length (nm)	Mean output power (mW)	Seconds per treatment spot (s)	Joules per treatment spot (J)	Number of spots treated	Number of sessions/Weeks	Dose recommended by WALT
Patellar tendinopathy							
Liu 2014[60]	810	200	600	-	1	24/4	Yes
	810	200	300	-	2*		
Stergioulas 2003[61]	904	50	300	1.2	10	10/2	Yes
Achilles tendinopathy							
Darre 1994[62]	830	30	-	4	4	12/2.5	Yes
Naterstad[63] (unpublished)	904	60	50	3	6	12/4	Yes
Stergioulas 2008[64]	820	30	-	0.9	6	12/8	Yes
Tumilty 2008[65]	810	100	30	3	6	12/4	Yes
Tumilty 2012[66]	810	7	30	0.21	6	12/4	No
Plantar fasciitis							
Basford 1998[67]	830	30	-	-	3 *	12/4	Unclear
Cinar 2017[68]	830	100	80	5.6	5	10/3	Yes
Cinar 2018[69]	830	100	80	5.6	5	10/3	Yes
Elsehrawy 2018[70]	830	-	-	-	3 *	6/3	Unclear
Kiritsi 2010[71]	904	60	-	8.4	1	18/6	Yes
	904	60	-	-	2 *		
Koteeswaran 2020[72]	830	-	180	-	3	9/3	Unclear
Lamba 2013[73]	820	100	80	-	3 *	12/4	Yes
Macias 2015[74]	635	17	600	-	3	6/3	Unclear
Sanmak 2019[75]	685	30	60	-	2 *	12/4	Unclear
Ulusoy 2017[76]	830	50	200	-	3 *	15/3	Yes
Yüzer 2006[77]	904	-	30	-	-	10/1.4	Unclear

*One or more spots/areas treated with movement of the laser probe.
LLLT, Low-Level Laser Therapy; WALT, World Association for Laser Therapy.

Overall pain and disability results pain and disability - LLLT versus any control

Data allowing for a meta-analysis of an immediate pain change were available from 16 trials with recommended, non-recommended or unknown laser dosing.

Overall, pain was significantly reduced by LLLT over any control immediately after completed therapy therapy (13.15 mm VAS (95% CI: 7.82 to 18.48), I^2 = 65%, N = 784) (Figure 2) and at follow-ups 4-12 weeks later (12.56 mm VAS (95% CI: 5.69 to 19.42), I^2 = 48%, N = 556) (Figure 3).

Overall, the disability results immediately after completed therapy significantly favoured LLLT over any control (SMD = 0.39 (95% CI: 0.09 to 0.7), I^2 = 30%, N = 260) (Figure 4). A disability reduction by LLLT remained significant at follow-ups 4-9 weeks after completed therapy (SMD = 0.32 (95% CI: 0.05 to 0.59), I^2 = 4%, N = 222) (Figure 5).

Figure 2 Overall pain results immediately after completed therapy - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure 3 Overall pain results at follow-ups - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure 4 Overall disability results immediately after completed therapy - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S = stretching; TU, Therapeutic Ultrasound.

Figure 5 Overall disability results at follow-ups - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Overall and subgroup pain results - LLLT versus placebo-control

Overall, pain was significantly reduced by LLLT over placebo-control immediately after completed therapy (11.48 mm VAS (95% CI: 2.68 to 20.28), I^2 = 73%, N = 507) (Figure 6) and during follow-ups 4-8 weeks after completed therapy (13.62 mm VAS (95% CI: 2.18 to 25.06), I^2 = 68%, N = 277) (Figure 3).

The recommended laser doses significantly reduced pain compared with placebo immediately after completed therapy (14.98 mm VAS (95% CI: 3.74 to 26.22), I^2 = 67%, N = 367) (Figure 6). A non-recommended laser dose from a single trial provided no significant pain reduction immediately after completed therapy (-3.0 mm VAS (95% CI: -11.17 to 5.7), N = 40) (Figure 6). Trials with unknown laser doses significantly favoured LLLT over placebo-control immediately after completed therapy (10.83 mm VAS (95% CI: 2.44 to 19.21), N = 100). The between-subgroup difference was significant (P = 0.02) (Figure 6).

At follow-ups 4-8 weeks after completed therapy, the recommended laser doses significantly reduced pain compared with placebo (14.00 mm VAS (95% CI: 2.81 to 25.19), I^2 = 5%) (supplementary material). A non-recommended dose provided in a single trial did not significantly reduce pain compared with placebo at follow-up 8 weeks after completed therapy (0.00 mm VAS (95% CI: -7.62 to 7.62), N = 40) (supplementary material). At follow-ups 4-5 weeks after completed therapy, trials with unknown laser doses demonstrated a significant pain reduction by LLLT compared with placebo (23.94 mm VAS (95% CI: 14.39 to 33.48), I^2 = 0%, N = 97) (supplementary material). The between-subgroup difference was significant (P = 0.0005) (supplementary material).

Figure 6 Subgroup pain results immediately after completed therapy - LLLT versus placebo-control
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Subgroup pain results - LLLT versus no intervention

Pain was significantly lowered by the recommended laser doses when used as an adjunct to exercise, stretching and insoles over exercise, stretching and insoles alone, both immediately after completed therapy (18.15 mm VAS (95% CI: 10.55 to 25.76), I^2 = 0%, N = 104) (Figure 7) and at follow-up 9 weeks after completed therapy (19.67 mm VAS (95% CI: 5.16 to 34.18), I^2 = 0%, N = 80) (supplementary material).

Figure 7 Subgroup pain results immediately after completed therapy - LLLT versus no intervention
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Overall and subgroup pain results - LLLT versus other interventions

Overall, pain was significantly reduced by LLLT compared with other interventions immediately after completed therapy (13.23 mm VAS (95% CI: 4.07 to 22.39), I^2 = 66%, N = 173) (Figure 8). Follow-up results of pain 4-12 weeks after completed therapy favoured LLLT over other interventions, but not significantly (9.41 mm VAS (95% CI: -0.44 to 19.26), I^2 = 16%, N = 193) (supplementary material).

The recommended laser doses were compared with exercise therapy in one trial and ESWT in another trial immediately after completed therapy and the pain results favoured LLLT, but not significantly (13.91 mm VAS (95% CI: -1.34 to 29.15), I^2 = 65%, N = 63) (Figure 8).

The pain results from three trials with unknown laser doses, in which two groups received extracorporeal shock wave therapy (ESWT) and one group received therapeutic ultrasound,

favoured LLLT immediately after completed therapy, but not significantly (12.88 mm VAS (95% CI: -1.29 to 27.04), I^2 = 77%, N = 110) (Figure 8).
At follow-ups 4-9 weeks after completed therapy, pain was significantly lowered by the recommended laser doses compared with other interventions (15.90 mm VAS (95% CI: 2.30 to 29.51), I^2 = 0%, N = 103) (supplementary material). Pain was not significantly lowered by unknown laser doses compared with other interventions at follow-ups 4-12 weeks after completed therapy (2.93 mm VAS (95% CI: -15.80 to 21.67), I^2 = 52%, N = 87) (supplementary material).

Figure 8 Overall and subgroup pain results - LLLT versus other interventions
ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S = stretching; TU, Therapeutic Ultrasound.

Overall and subgroup disability results - LLLT versus placebo-control
Overall, the disability results favoured LLLT over placebo-control immediately after completed therapy, but not significantly (SMD = 0.2 (95% CI: -0.18 to 0.58), I^2 = 0%, N = 107) (Figure 4). The same applied to the follow-up results 4-8 weeks after completed therapy (SMD = 0.19 (95% CI: -0.11 to 0.49), I^2 = 0%, N = 173) (supplementary material).

The disability results immediately after completed therapy favoured the recommended laser doses over other interventions, but not significantly (SMD = 0.25 (95% CI: -0.21 to 0.7), I^2 = 0%, N = 76) (supplementary material). The same applied to unknown laser doses compared with placebo-control immediately after completed therapy (SMD = 0.10 (95% CI: -0.61 to 0.80), N = 31) (supplementary material).

At follow-ups 4-8 weeks after completed therapy, the disability results favoured the recommended laser doses over other interventions, but not significantly (SMD = 0.24 (95% CI: -0.21 to 0.70), I^2 = 0%, N = 76) (supplementary material). The same applied to the unknown laser doses compared with placebo-control immediately after completed therapy (SMD = 0.14 (95% CI: -0.26 to 0.54), N = 107) (supplementary material).

Overall and subgroup disability results - LLLT versus other interventions
The overall disability results immediately after completed therapy favoured LLLT, but not significantly (SMD = 0.58 (95% CI: -0.11 to 1.27), I^2 = 56%, N = 90) (figure 4).

The recommended laser doses neither provided a significant disability reduction compared with other interventions immediately after completed therapy (SMD = 0.20 (95% CI: -0.85 to 1.25), N = 14) (supplementary material). The same applied to unknown laser doses compared with other interventions immediately after completed therapy (SMD = 0.73 (95% CI: -0.26 to 1.72), N = 76) (supplementary material).

Subgroup disability results - LLLT versus no intervention
The disability results of the recommended laser doses applied as an adjunct to exercise therapy or stretching immediately after completed therapy favoured LLLT, but not significantly (SMD = 0.68 (95% CI: -0.49 to 1.85), I^2 = 69%, N = 61) (supplementary material). At follow-up 9 weeks after completed therapy, disability was significantly lowered by the recommended laser doses as an adjunct to stretching and insoles compared with exercise therapy and insoles alone (SMD = 0.82 (95% CI: 0.24 to 1.41), N = 49) (supplementary material).

Sensitivity analysis of laser dose categorisation
The irradiation procedure by Darre et al.[62] was judged as a recommended laser dose, based on the reported dose parameters in the paper. However, the dose description is somewhat sparse and could be misinterpreted. If the study by Darre et al. was allocated to the unknown laser dose subgroup, the

statistical heterogeneity would be eliminated in the recommended laser dose group and the estimated pain reduction would be increased to 21.12 mm VAS ((95% CI: 14.94 to 27.31), $I^2 = 0\%$, N = 278) versus placebo immediately after completed therapy (supplementary material).

Risk-of-bias within studies

Ten of the included trials were found to be of high methodological quality, and the remaining eight included trials were found to be of moderate methodological quality (Table 3). All the trials featured adequate randomisation. Allocation concealment was sufficient in 11 (61%) of the trials. The groups were similar at baseline in 15 (83%) of the trials. The participants were blinded in nine (50%) of the trials. The therapists were blinded in five (28%) of the trials, all of which were placebo-controlled. The assessors were blinded in seven (39%) of the trials, all of which were placebo-controlled. Outcome data were available from more than 15% of the participants in 14 (78%) of the trials. An intention-to-treat analysis was used in 10 (56%) of the trials. A between-group statistical comparison was performed in all the trials. Point measures and variability outcome data were stated in 17 (94%) of the trial reports.

The lack of therapist and assessor blinding were the two most obvious methodological inadequacies. However, risk-of-bias subgroup analyses performed post-hoc revealed that there was no significant interaction between the effect estimates and the lack of blinding (supplementary material).

Risk-of-bias across studies (small study/publication bias)

In a random effects model, small and large trials are weighted relatively even when statistical heterogeneity is present. In a fixed effects model, the heterogeneity is ignored and will not influence the weights. Smaller studies in meta-analyses tend to show more positive results than larger trials.[79] However, there was almost no difference between the pain results of the two meta-analysis models, indicating that no small study bias exists (supplementary material). Likewise, there was no obvious asymmetry in a funnel plot based on the same meta-analyses of pain, indicating that no publication bias was present (supplementary material).

Table 3 PEDro score

Study ID	**Item number**											**Total**	**Quality**
	1*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Basford 1998[67]	+	+	-	+	+	-	+	+	-	+	+	7	High
Cinar 2017[68]	+	+	+	+	-	-	-	+	+	+	+	7	High
Cinar 2018[69]	+	+	+	+	-	-	-	+	+	+	+	7	High
Darre 1994[62]	+	+	+	-	+	+	-	-	-	+	-	5	Moderate
Elsehrawy 2018[70]	+	+	-	+	-	-	-	+	-	+	+	5	Moderate
Kiritsi 2010[71]	+	+	+	+	+	+	+	-	-	+	+	8	High
Koteeswaran 2020[72]	+	+	-	+	-	-	-	+	+	+	+	6	Moderate
Lamba 2013[73]	+	+	-	+	+	-	-	+	-	+	+	6	Moderate

Liu 2014[60]	+	+	-	+	-	-	-	+	+	+	+	6	Moderate
Macias 2015[74]	+	+	+	+	+	-	+	+	+	+	+	9	High
Naterstad[63] (unpublished)	+	+	+	+	+	+	+	+	+	+	+	10	High
Sanmak 2019[75]	+	+	+	+	-	-	-	+	+	+	+	7	High
Stergioulas 2003[61]	+	+	-	+	+	-	+	-	-	+	+	6	Moderate
Stergioulas 2008[64]	+	+	+	+	+	-	-	-	+	+	+	8	High
Tumilty 2008[65]	+	+	+	+	+	+	+	+	+	+	+	10	High
Tumilty 2012[66]	+	+	+	+	+	+	+	+	+	+	+	10	High
Ulusoy 2017[76]	+	+	-	+	-	-	-	+	-	+	+	5	Moderate
Yüzer 2006[77]	+	+	+	+	-	-	-	-	-	+	+	5	Moderate

PEDro, Physiotherapy Evidence Database.
*Item not included in the mean score.
1. Eligibility criteria specified.
2. Random allocation.
3. Concealed allocation.
4. Groups similar at baseline.
5. Subject blinding.
6. Therapist blinding.
7. Assessor blinding.
8. Less than 15% dropout.
9. Intention-to-treat analysis.
10. Between-group statistical comparisons.
11. Point measures and variability data.

DISCUSSION

We investigated the effectiveness of LLLT in tendon and aponeurosis disorders of the lower extremity. Our overall meta-analysis results demonstrated that pain and disability were statistically significantly reduced by LLLT compared with any control both immediately after completed therapy and in the follow-up period, that is, 4-12 weeks after completed therapy for pain and 4-8 weeks after completed therapy for disability.

Like in our previous meta-analysis of LLLT in knee osteoarthritis[42], we sub-grouped the included trials in the current review using the WALT treatment recommendations.[58 59] Compared with placebo-control, the recommended laser doses in the current review generally had a larger pain-relieving effect than non-recommended laser both immediately after therapy and in the follow-up period. Similarly, the recommended laser doses had a significant pain-relieving effect as an adjunct to exercise therapy, stretching and insoles both immediately after completed therapy and in the follow-up period. Compared with other treatment modalities, the recommended laser doses were significantly superior, but only at follow-up and only as a pain treatment.

The minimal clinically important improvement (MCII) for pain expressed on the VAS or NRS has not been established for tendinopathy in the lower extremity[80], even though pain is a prominent feature of this condition. A MCII of 14 mm on a VAS has been suggested in rotator cuff tendinopathy[81], which could indicate that the pain reduction from recommended LLLT doses,

compared with placebo-LLLT, is both statistically significant and clinically relevant at the end of treatment (14.98 mm) and at follow-ups (14.0 mm). Prior research indicates that there is a difference in central sensitisation in upper- and lower limb tendinopathy[82], and thus the transference of MCII from rotator cuff tendinopathy should be considered with some caution. In plantar fasciitis, the MCII for VAS pain has been estimated to be 8 mm for average pain[83], and our results are above this threshold in all comparisons.

As for disability, we found that LLLT overall had a small significant effect both immediately after completed therapy and in the follow-up period. Compared with placebo, there were no significant effect of LLLT on disability immediately after completed therapy and at follow-ups. Only Cinar et al.[68] provided follow-up data on disability regarding LLLT as an add-on to exercise therapy. They found a large and significant positive effect on disability 12 weeks after completed therapy, however, their results are based only on 49 participants[68], and thus this meta-analysis result should be interpreted with caution.

We were unable to dose categorise the study by Macias et al.[74] since they used a laser within the visible spectrum (635 nm), which is not mentioned in the WALT treatment guidelines. Light in the red wavelengths (600-700 nm) penetrates the tissue to a lesser extent than light with a wavelength of 700-1000 nm.[84] Macias et al. utilized a relatively low mean output power, but they stated that they irradiated the tissue for 600 seconds and achieved a significant pain reduction. The methodological quality of their trial[74] was categorised as high, with a PEDro score of 9.

Sanmak et al.[75] also used a laser within the red spectrum, but they provided a much smaller dose. Sanmak et al.[75] compared LLLT with ESWT in plantar fasciitis and found no difference between the groups regarding pain immediately after treatment, but an insignificant better result for ESWT 4 weeks after completed treatment. Comparing LLLT to ESWT, we would expect different time-profiles for pain alleviation, as the effect of ESWT might be better at later time-points.[85] Sanmak et al.[75] applied LLLT in a circular motion on the insertion site of the plantar fascia for 60 seconds and along the fascia for another 60 seconds. They stated that they irradiated the tissue with 2 J/cm^2, which according to our calculation (Watt*seconds) corresponds to a relatively low mean output power of 18 mW/cm^2. Moving the laser probe during irradiation will yield a smaller laser dose per spot, and larger movement will for instance reduce the energy delivered per cm^2. Additionally, the skin underneath the heel is thick[86], and thus absorbs a large percentage of the laser.

We did not identify any trials focusing on trochanter tendinopathy, peroneal or tibialis posterior tendinopathy. In a double-blinded randomised trial by Lögdberg-Andersson et al.[87], the effect of a 904 nm wavelength laser on participants with trochanteritis was investigated. They found a significant positive effect compared with placebo on pain expressed on a VAS and with algometry, both at the end of treatment and four weeks after.[87] This trial was not included in our review as we were unable to isolate the participants of interest.

We were only able to identify two randomised controlled trials regarding the effect of LLLT compared with a control in patellar tendinopathy. In a recent clinical trial by Ashok et al.[88], the effect of LLLT was compared to that therapeutic ultrasound in persons with patellar tendinopathy. They found a statistically significant effect of LLLT compared with therapeutic ultrasound, both in pain reduction and function, however, this trial is small (N = 8) and only of moderate methodological quality. This is consistent with the findings in this review. Another LLLT trial by Meier et al.[89] included participants with both patellar tendinopathy (N = 58) and Achilles tendinopathy (N = 52), however, we did not include this trial as it solely concerned the effects of an invisible (904 nm wavelength) laser versus a red (632 nm wavelength) laser. They stated that the red laser was placebo but delivered a laser dosage that would be considered possibly effective. Both groups had a positive effect on a combined index of pain and function, favouring the 904 nm laser,

but the trial does not provide point measures or variability data, among other methodological challenges.

The presence and role of inflammation in chronic tendinopathy has been an ongoing debate in the last few decades. There is currently increased support that inflammation has a causal role in tendinopathy, where immune cells and molecular mediators are included as inflammatory components.[90-92] Prostaglandin E_2 (PGE_2) has been suggested to sustain inflammation and pain in human tendon disease.[93] In Achilles tendinopathy, a reduction of PGE_2 and a concurrent increased pain pressure threshold after LLLT has been found in a double-blinded randomised trial by Bjordal et al.[94], where microdialysis of the tendon was performed in seven participants. The participants had aggravated the symptoms through a pain inducing activity immediately prior to the examination. Only the immediate (105 minutes) response to LLLT was investigated in the trial, but the findings support the notion that LLLT may act anti-inflammatory in Achilles tendinopathy.

Several authors of the included trials failed to give an adequate description of the laser dose parameters used. A LLLT dose-response relationship has been established in systematic reviews of tendinopathy[35-37] and osteoarthritis.[42] In the current review, some of the statistical heterogeneity is plausibly due to the variation in applied laser doses. The statistical heterogeneity of the dose subgroup analyses was generally lower than in the overall (any dose) analyses and this indicates that the dose might be more important for the effect than the location of the tendinopathy. The only study that caused noteworthy statistical heterogeneity in the dose subgroup analysis with placebo-control was the one by Darre et al.[62] Most of the pain and disability analyses comparing LLLT with other interventions were performed on plantar fasciitis, and yielded a moderate level of statistical heterogeneity, and it may be explained by the variation in control interventions.

The included trials had a moderate to high methodological quality (mean PEDro score = 7.1). Therapist and assessor blinding lacked in many of the included studies, however, the lack of blinding was not significantly associated with higher effect estimates (supplementary material).

Future trials should be conducted to directly compare the effectiveness of different LLLT parameters. Additionally, systematic reviews of LLLT should include dose-response investigations.

Strengths and limitations of this study

This review was conducted in conformance with a detailed a priori published protocol, which includes, for example, a plan for subgrouping the trials by laser dose. The review includes results from two studies reported in non-English language[62 77] and an unpublished study.[63] The review features meta-analyses with direct comparisons between LLLT and placebo LLLT, other interventions and no intervention. Although only one reviewer extracted data from the included trials, the extracted data was checked for correctness by another reviewer.

CONCLUSIONS

LLLT reduces pain in lower extremity tendinopathy and plantar fasciitis compared with placebo, other treatments and as an add-on to exercise therapy. LLLT reduces disability to a small extent in the patients. Adhering to the WALT dose recommendations is advised.

Author contributions IFN and MBS wrote the PROSPERO protocol. IFN and MBS selected the trials, with the involvement of JJ when necessary. IFN and MBS judged the risk-of-bias, with the involvement of JJ when necessary. IFN and MBS extracted the data. IFN and MBS translated the non-English articles. IFN performed the analyses, under supervision by MBS. IFN, JJ, JMB, CC, RABLM and MBS participated in interpreting of the results. IFN drafted the first version of the manuscript, and subsequently revised it, based on comments by JJ, JMB, CC, RABLM and MBS. All authors read and accepted the final version of the manuscript.

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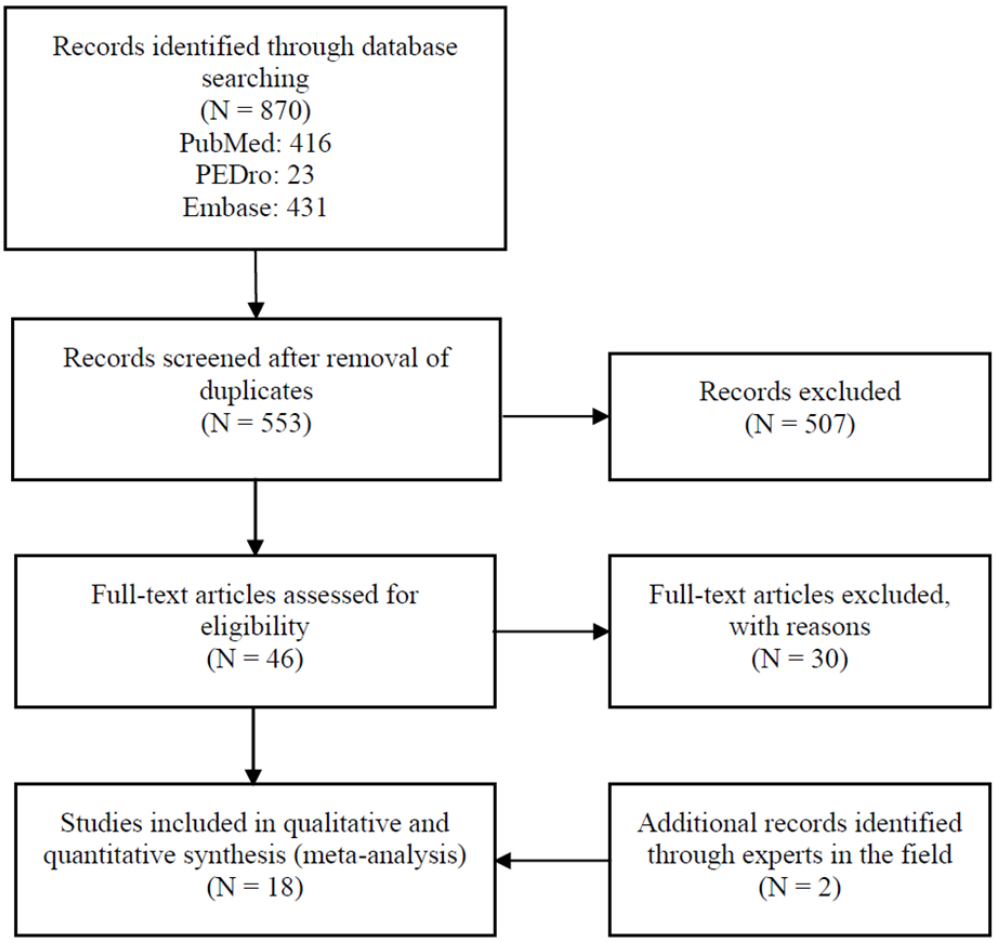

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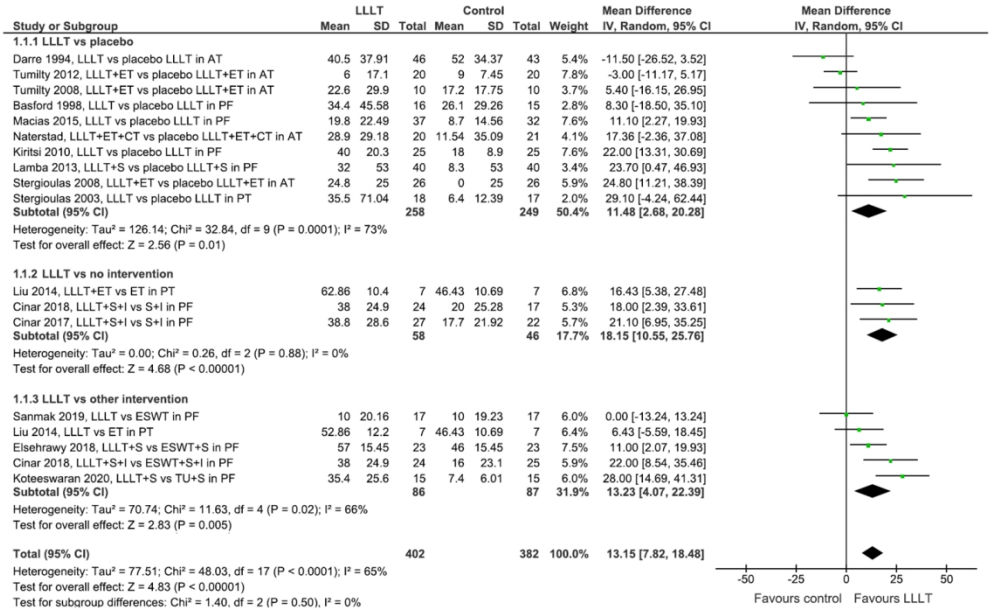

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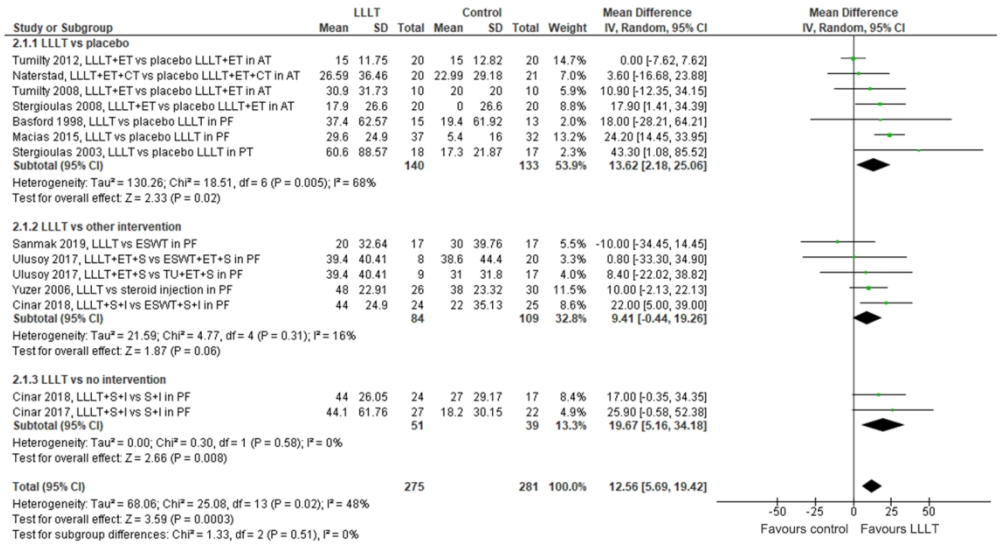

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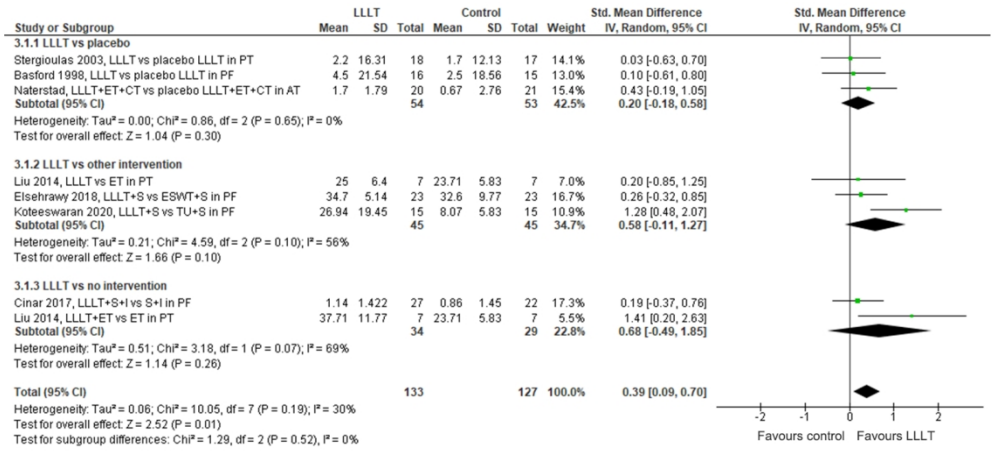

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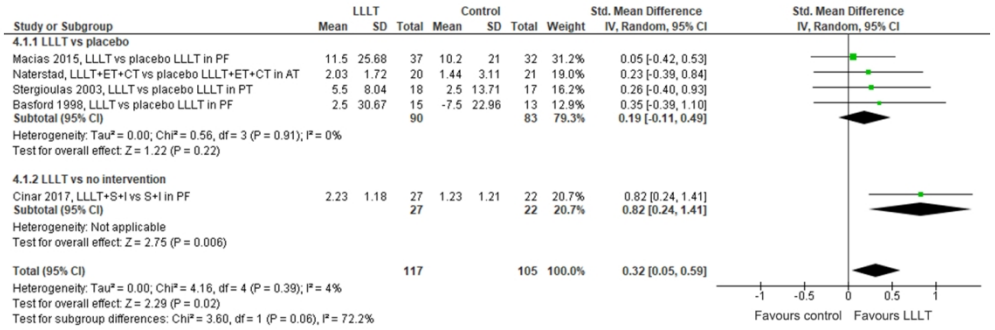

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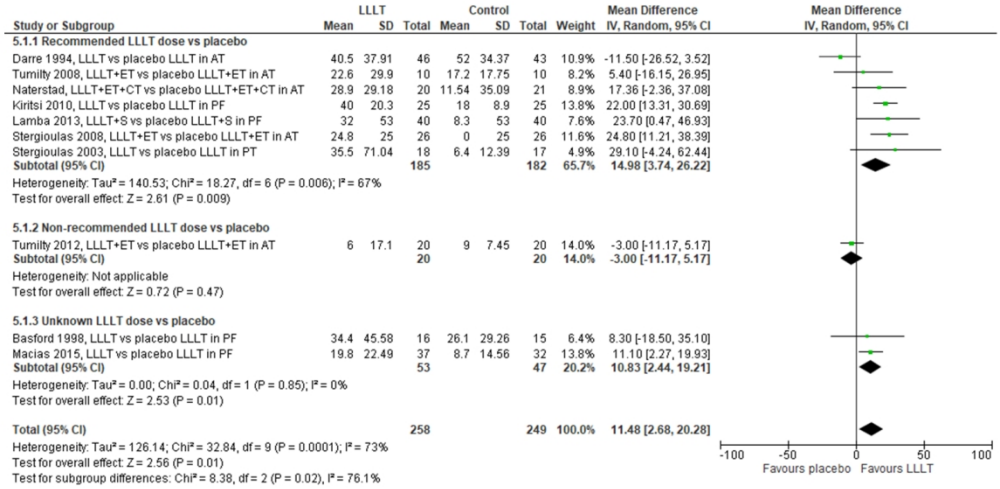

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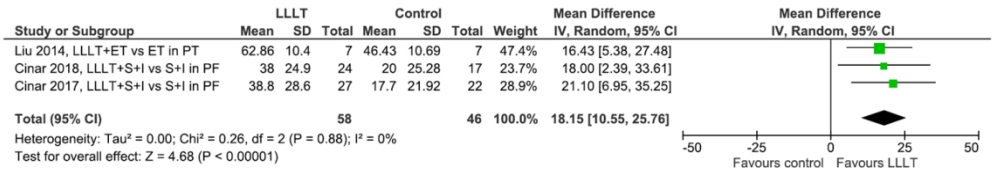

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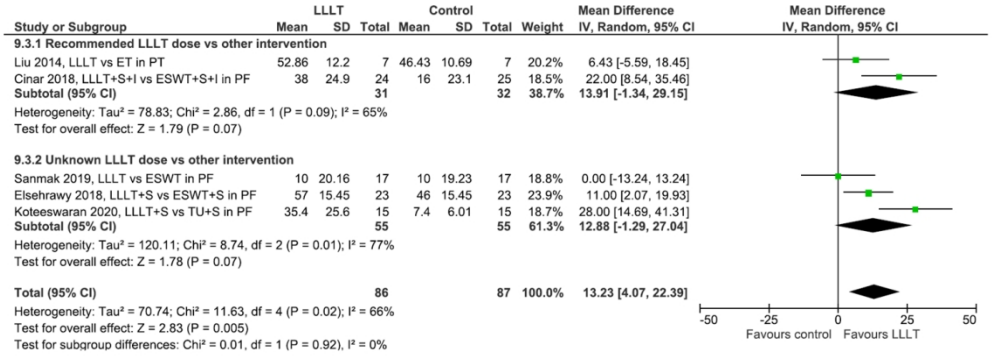

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Supplemental digital content for the article:

Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

Contents

PubMed database search string

("Low-Level Light Therapy"[Mesh] OR LLLT[Title/Abstract] OR "low level"[Title/Abstract] OR "low power"[Title/Abstract] OR laser therap*[Title/Abstract] OR "laser acupuncture"[Title/Abstract] OR "HeNe"[Title/Abstract] OR "632 nm"[Title/Abstract] OR "Ga-Al-As"[Title/Abstract] OR "820 nm"[Title/Abstract] OR "830 nm"[Title/Abstract] OR "850 nm"[Title/Abstract] OR "GaAs"[Title/Abstract] OR "904 nm"[Title/Abstract] OR Photobiomodulation[Title/Abstract] OR phototherap*[Title/Abstract]) and ("Tendinopathy"[Mesh] or tendi*[Title/Abstract] or tendo*[Title/Abstract] or "plantar fasciitis"[Title/Abstract] or "Fasciitis, Plantar"[Mesh] or "Policeman's Heel"[Title/Abstract] or "Iliotibial Band Syndrome"[Mesh] or Iliopsoas tendi*[Title/Abstract] or Jumper*[Title/Abstract] or Patella[Title/Abstract] or Achill*[Title/Abstract] or "Achilles Tendon"[Mesh])

Table of excluded full text articles

Author/Year/Reference	**Reasons for exclusion**
Abat et al. 2016[1]	Impossible to isolate effect, combined treatments compared with other treatment
Aigner et al. 1996[2]	No control group
Ashok et al. 2018[3]	Lacks randomisation
Atik et al. 2018[4]	Commentary only
Bjordal et al. 2006[5]	Outcomes of interest not reported
Chang et al. 2015[6]	Outcomes of interest not reported
Cinar et al. 2013[7]	Conference paper only (author contacted)
Cinar et al. 2012[8]	Solely abstract available
Costantino et al. 2005[9]	Not LLLT, high intensity laser therapy
Coughlin et al. 2014[10]	Solely abstract available
Fernandes et al. 1991[11]	Mixed population with unclear inclusion of diagnosis
Foley et al. 2016[12]	Not LLLT, light emitting diode therapy
Jastifer et al. 2014[13]	No control group
Lögdberg-Andersson et al. 1994[14]	Only pooled data on lower and upper extremity available
Mardh et al. 2016[15]	Not LLLT, high intensity laser therapy
Meier et al. 1988[16]	Outcomes of interest not reported
Morimoto et al. 2013[17]	No control group
Mulcahy et al. 1995[18]	Lacks credible control group, includes only 3 patients with tendinopathy
Notarnicola et al. 2014[19]	Not LLLT, high intensity laser therapy
Olivera et al. 2009[20]	Animal study
Orellana-Molina et al. 2010[21]	Outcomes of interest not reported
Saxena et al. 2015[22]	Not LLLT
Scott et al. 2011[23]	Review
Siebert et al. 1987[24]	Mixed population/diagnoses
Simunovic 1996[25]	Narrative review
Suleymanoglu et al. 2014[26]	Conference abstract
Takla et al. 2019[27]	Used a combination of LLLT and light emitting diode therapy
Tumilty et al. 2015[28]	Conference abstract
Tumilty et al. 2016[29]	Not LLLT, high intensity laser therapy

LLLT, low-level laser therapy.

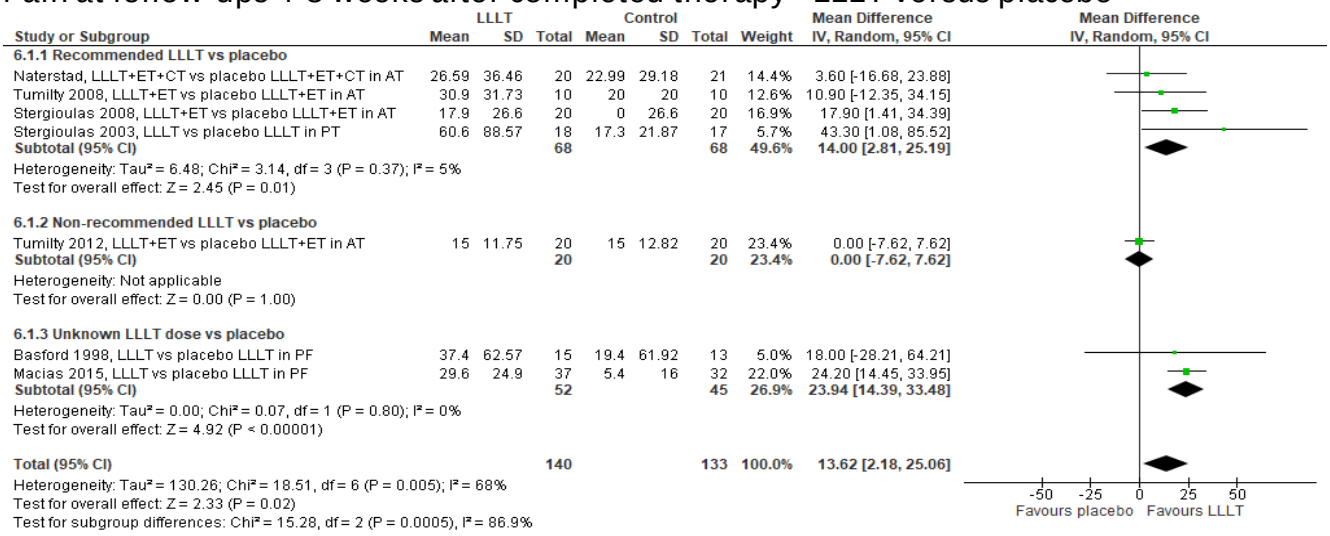

Figure S1: Pain at follow-ups 4-8 weeks after completed therapy - LLLT versus placebo
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

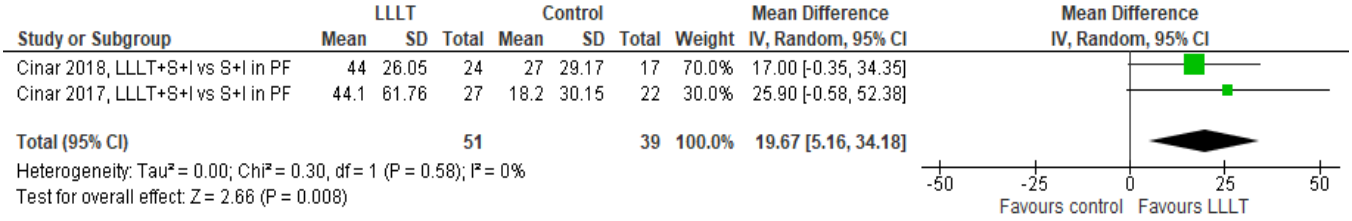

Figure S2: Pain at follow-ups 8 weeks after completed therapy - LLLT versus no intervention
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; S, stretching.

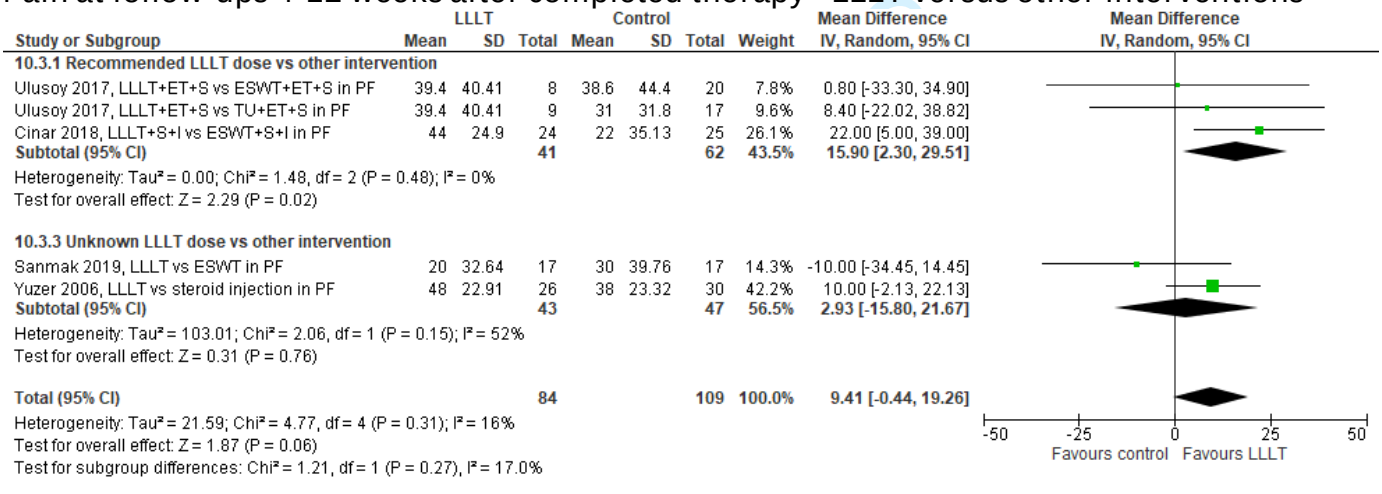

Figure S3: Pain at follow-ups 4-12 weeks after completed therapy - LLLT versus other interventions
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Disability immediately after completed therapy - LLLT versus placebo

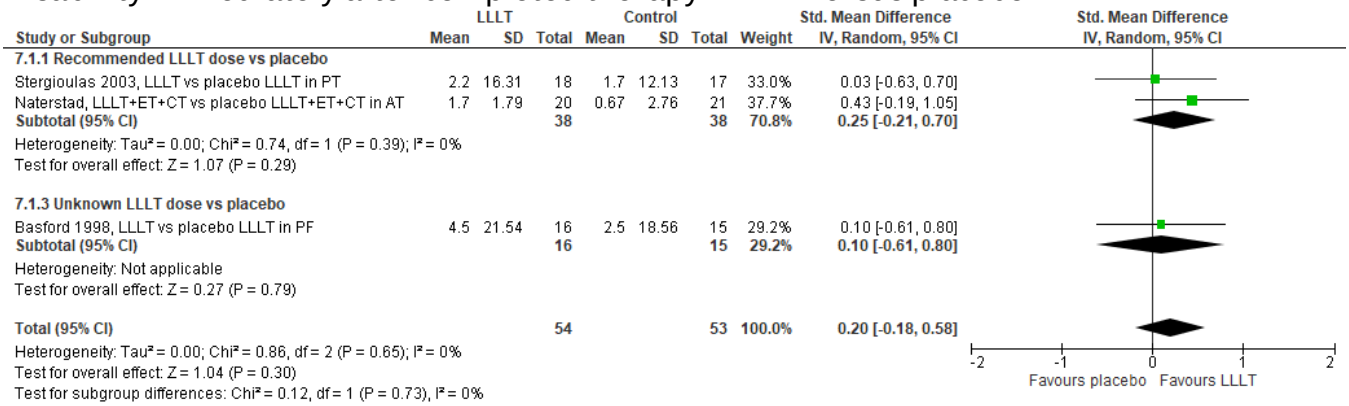

Figure S4: Disability immediately after completed therapy - LLLT versus placebo
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy.

Disability at follow-ups 4-8 weeks after completed therapy - LLLT versus placebo

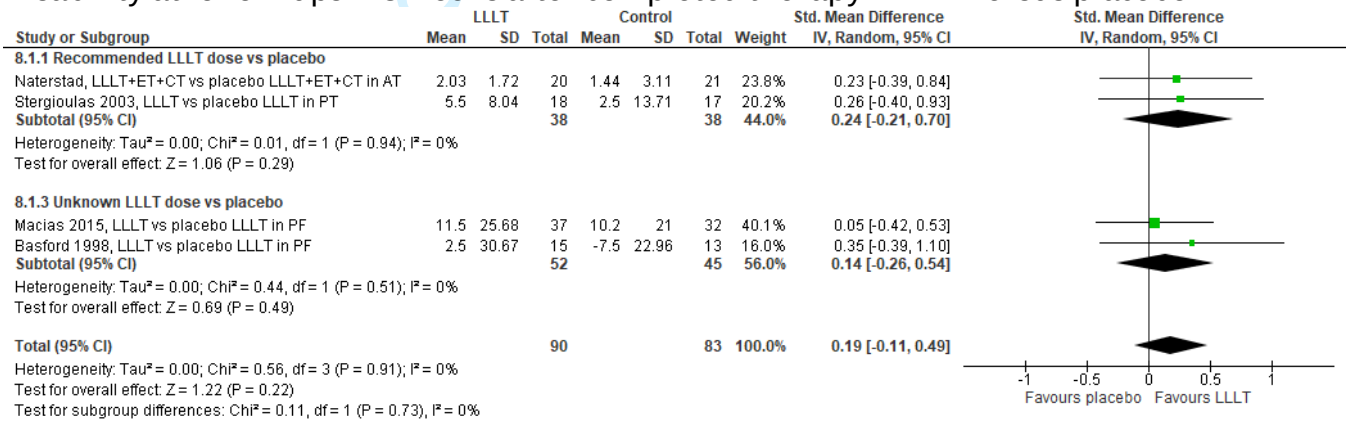

Figure S5: Disability at follow-ups 4-8 weeks after completed therapy - LLLT versus placebo
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy.

Disability immediately after completed therapy - LLLT versus other interventions

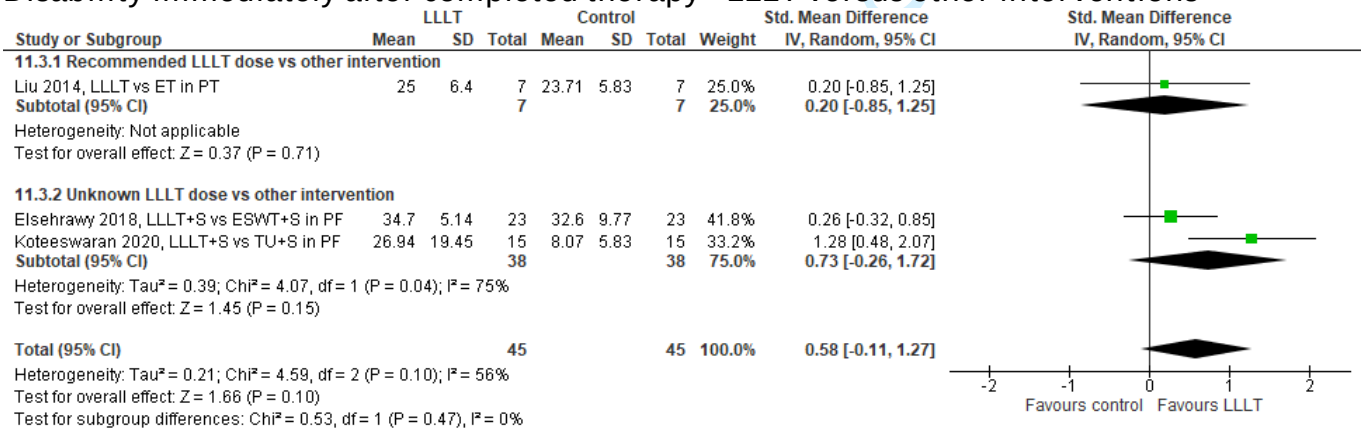

Figure S6: Disability immediately after completed therapy - LLLT versus other interventions
ET, exercise therapy; ESWT, Extracorporeal Shock Wave Therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

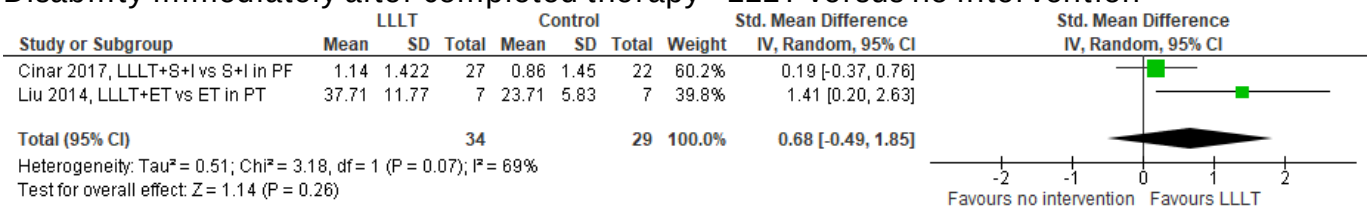

Figure S7: Disability immediately after completed therapy - LLLT versus no intervention
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Figure S8: Disability at follow-up 9 weeks after completed therapy - LLLT versus no intervention
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Sensitivity analyses

Allocating the study by Darre et al. 1994 to the unknown laser dose subgroup eliminates the statistical heterogeneity in the recommended laser dose subgroup and increases the estimate of placebo-controlled pain reduction to 21.12 mm VAS ((95% CI: 14.94 to 27.31), I^2 = 0%, N = 278) immediately after completed therapy (Figure S9).

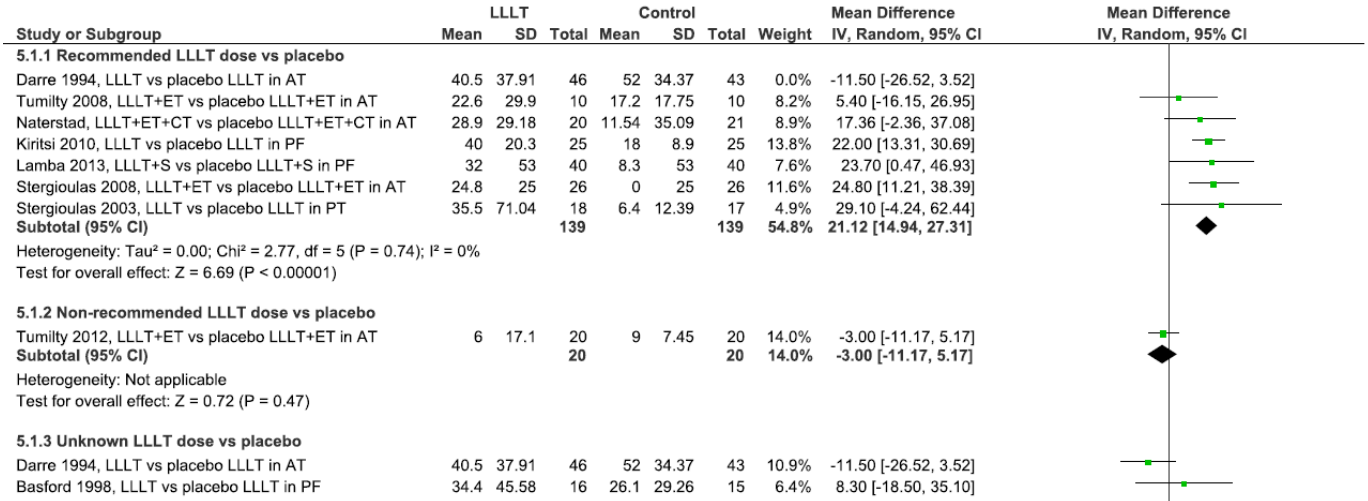

Figure S9: Alternative LLLT dose subgrouping
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Risk-of-bias within studies post-hoc analyses

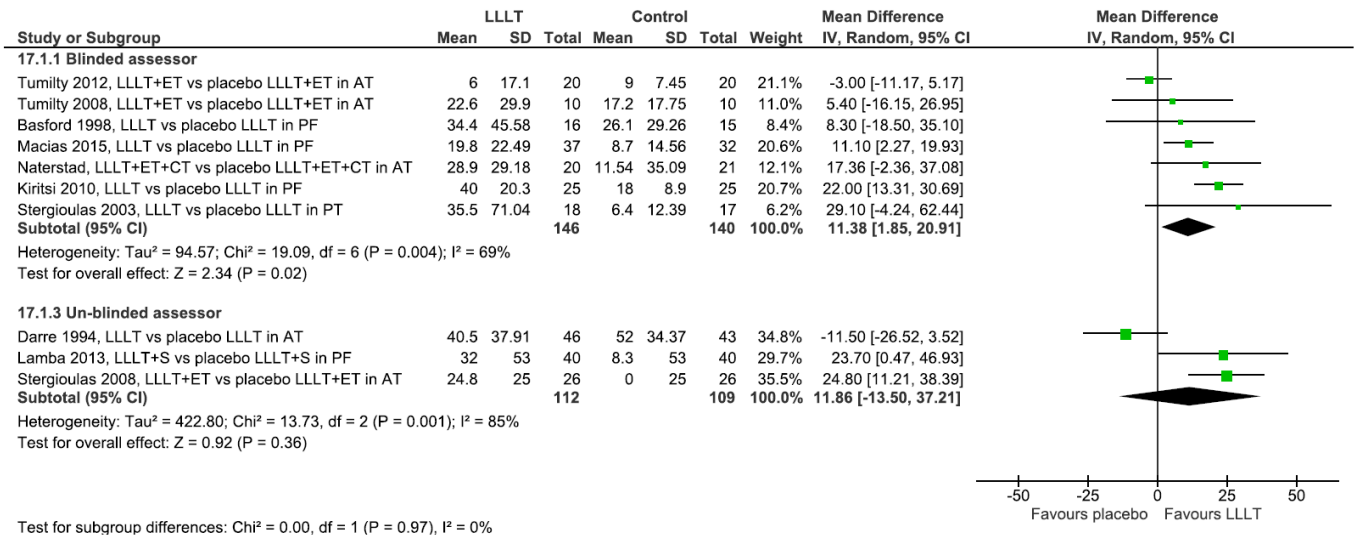

Figure S10: Blinded versus unblinded assessor
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

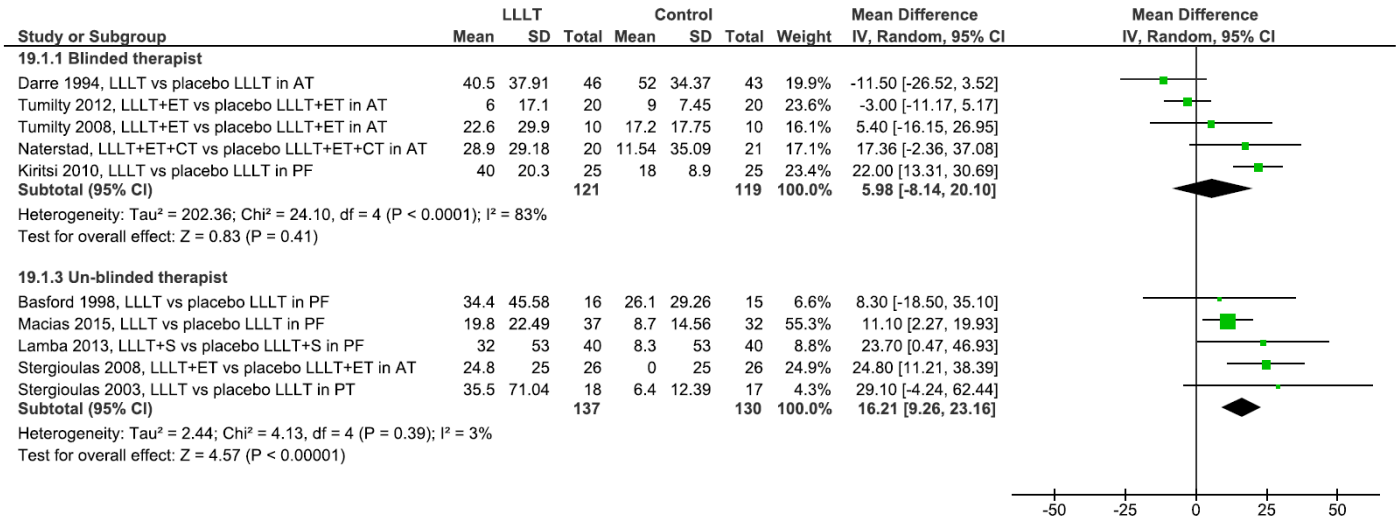

Figure S11: Blinded versus unblinded therapist
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Risk-of-bias across studies - random versus fixed effects meta-analysis results of pain

There was almost no difference between the pain point estimates of the random and fixed effects models (pain immediately after the end of therapy), that is, 11.48 mm versus 10.21 mm VAS, indicating that no small study bias exists (Figures S12 and S13).

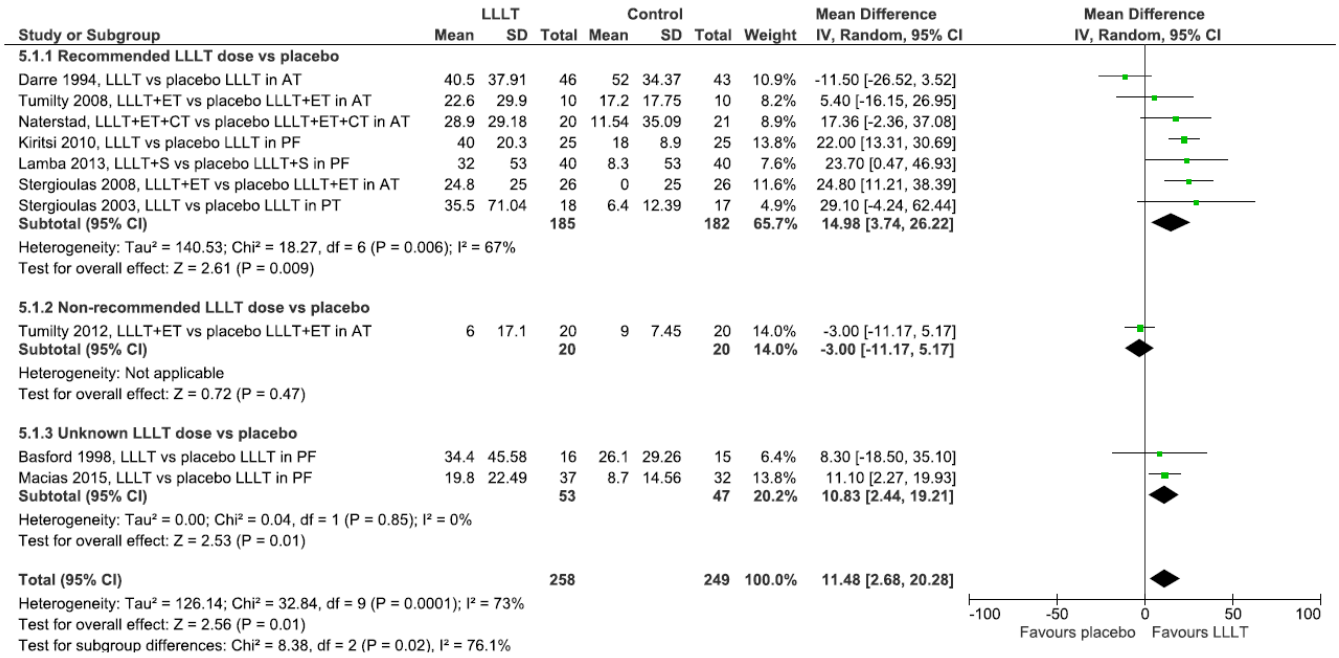

Figure S12: Random effects meta-analysis model

AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

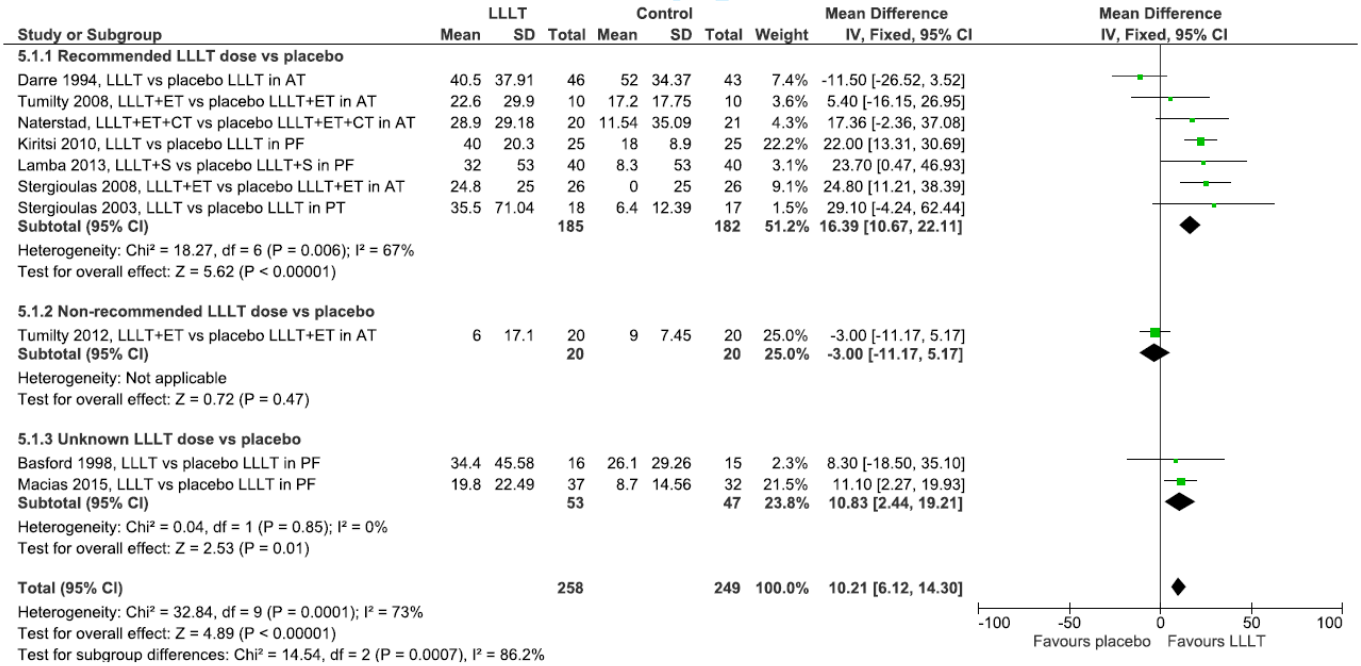

Figure S13: Fixed effects meta-analysis model

AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Risk-of-bias between studies - funnel plot

Funnel plot of pain results immediately after completed therapy indicating that publication bias is absent (Figure S14).

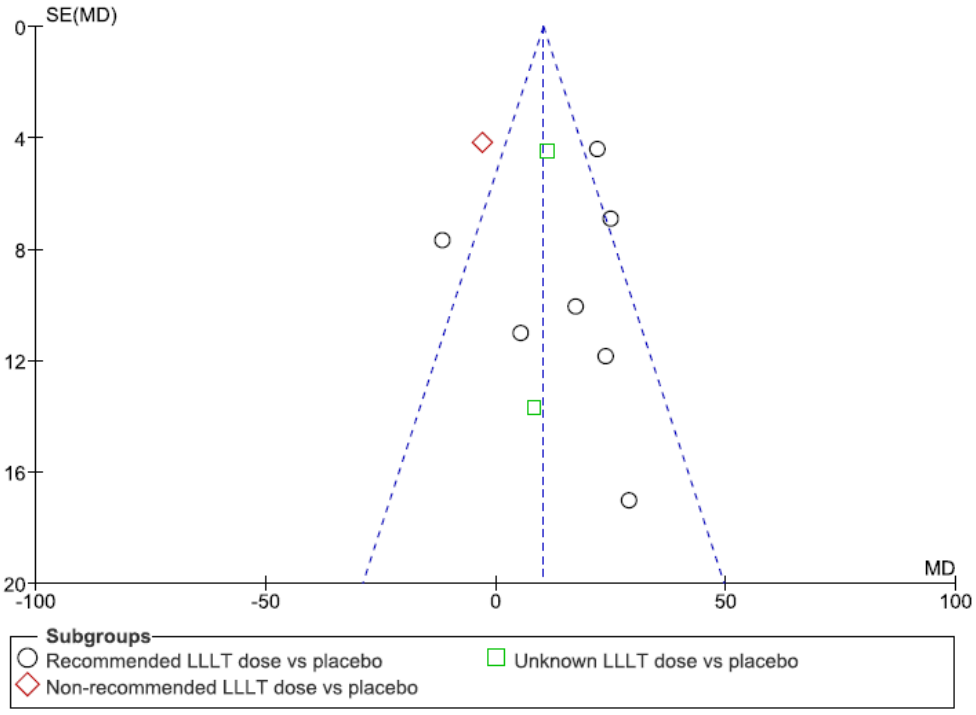

Figure S14: Funnel plot

LLLT, Low-Level Laser Therapy; MD, mean difference; SE, standard error.

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PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 3-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4

PRISMA checklist (continued)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 3 and 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 9-10 + supplementary material
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 4 + figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-2 and figure 2-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 10-11 and table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	figure 2-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 7-10 and figure 2-8 + supplementary material
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 10 and supplementary material
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 14

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Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

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Secondary Subject Heading:	Rehabilitation medicine, Pathology
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Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

Ingvill Fjell Naterstad[1], Jon Joensen[1], Jan Magnus Bjordal[1], Christian Couppé[2,3], Rodrigo Alvaro Brandão Lopes-Martins[4], Martin Bjørn Stausholm[1]

[1]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[2]Institute of Sports Medicine Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark
[3]Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[4] Post Graduate Program in Human Movement and Rehabilitation, Universidade Evangélica de Goiás, Anápolis, Brazil

Correspondence to: Ingvill Fjell Naterstad naterstad@gmail.comWord count: 4774

Abstract

Objectives We investigated the effectiveness of low-level laser therapy (LLLT) in lower extremity tendinopathy and plantar fasciitis on patient-reported pain and disability.

Design Systematic review and meta-analysis.

Data sources Eligible articles in any language were identified through PubMed, Embase and Physiotherapy Evidence Database (PEDro) on the 20th August 2020, references, citations and experts.

Eligibility criteria for selection of studies Only randomised controlled trials involving participants with lower extremity tendinopathy or plantar fasciitis treated with LLLT were included.

Data extraction and synthesis Random effects meta-analyses with dose subgroups based on the World Association for Laser Therapy (WALT) recommendations were conducted. Risk-of-bias was assessed with the PEDro scale.

Results LLLT was compared with placebo (10 trials), other interventions (5 trials) and as an add-on intervention (3 trials). The study quality was moderate to high.

Overall, pain was significantly reduced by LLLT at completed therapy (13.15 mm Visual Analogue Scale (VAS; 95% CI: 7.83-18.48)) and 4-12 weeks later (12.56 mm VAS (95% CI: 5.69-19.42)). Overall, disability was significantly reduced by LLLT at completed therapy (Standardised Mean Difference (SMD) = 0.39 (95% CI: 0.09-0.7) and 4-9 weeks later (SMD = 0.32 (95% CI: 0.05-0.59)). Compared with placebo-control, the recommended doses significantly reduced pain at completed therapy (14.98 VAS mm (95% CI: 3.74-26.22)) and 4-8 weeks later (14.00 mm VAS (95% CI: 2.81-25.19)). The recommended doses significantly reduced pain as an add-on to exercise therapy versus exercise therapy alone at completed therapy (18.15 mm VAS (95% CI: 10.55-25.76)) and 4-9 weeks later (15.90 mm VAS (95% CI: 2.3-29.51)). No adverse events were reported.

Conclusion LLLT significantly reduces pain and disability in lower extremity tendinopathy and plantar fasciitis in the short and medium term. Long-term data was not available. Some uncertainty about the effect size remains due to wide confidence intervals and lack of large trials.

PROSPERO registration number CRD42017077511

Keywords Phototherapy; Laser therapy; Tendinopathy; Plantar Fasciitis; Systematic review; Meta-analysis

Strengths and limitations of this study

- ► This review was performed in conformance with a prospective published protocol, which included a plan for subgrouping the trials by laser dose.
- ► There were no language restrictions; two (11%) of the included trials were reported in non-English language.
- ► The review includes results from an unpublished trial.
- ► The review features meta-analyses with direct comparisons between low-level laser therapy and placebo, other interventions, and no intervention.
- ► Only one reviewer extracted the data from the included trials, but the extracted data were checked for correctness by another reviewer.

INTRODUCTION

Tendinopathy and plantar fasciitis are disorders associated with substantial pain and loss of function in the lower extremity, especially prevalent in the athletic population but also common in the non-athletic population[1-3]. The aetiology of tendinopathy and plantar fasciitis is multifactorial and not fully understood. Risk factors for tendinopathy include overuse, acute trauma, ageing and genetic predisposition[4, 5]. Known risk factors for plantar fasciitis are prolonged standing and jumping, reduced ankle dorsiflexion and obesity[6-9]. Disorganised and degenerating collagen fibres, increased numbers of fibroblasts, altered composition of extracellular matrix proteins, formation of new vessels and rounding of tendon cells can be found in both tendinopathy and plantar fasciitis [10, 11].

Conservative treatment for lower extremity tendinopathy and plantar fasciitis includes an array of modalities and approaches. The effect of exercise therapy in tendinopathy is well-established, and any exercise type is preferential to wait-and-see in the earlier stages of tendinopathy [12]. However, a superiority of exercise therapy compared with other interventions has not been demonstrated. The use of non-steroidal anti-inflammatory drugs (NSAIDs) are frequently recommended in the early stages of tendinopathy and plantar fasciitis [13-15], even though the effectiveness of these drugs in lower extremity tendinopathies has only been investigated in a few placebo-controlled trials [16-20]. Moreover, NSAIDs have well known potentially fatal side-effects, most importantly severe cardiovascular events and gastrointestinal toxicity [21]. Low-level laser therapy (LLLT), also known as photobiomodulation therapy, is a quickly administered non-invasive intervention option free from negative side-effects. LLLT is an athermic photochemical modality, where red or near-infrared light is used to stimulate tissue healing and reduce pain and inflammation [22-25]. The working mechanisms of LLLT are partly established. There is evidence that LLLT increases adenosine triphosphate production[26], modulates the reactive oxygen species and the induction of transcription factors[27-30]. Furthermore, it has been demonstrated that LLLT inhibits cyclooxygenase-2 gene expression and prostaglandin E_2 (PGE_2) production in tendons[31, 32] and inhibits matrix metalloproteinase activity[32, 33]. In addition, under application of LLLT, macrophages are more likely to act as phagocytes[34].

There are heterogeneous results from clinical trials of LLLT on tendinopathies, and this may or may not be explained by a dose-response relationship[35-37]. Variation in LLLT parameters, such as wavelength, power density, pulse structure, application method and time-point of assessment may affect the treatment outcome. The World Association for Laser Therapy (WALT) has published treatment recommendations regarding the minimum LLLT doses required to reach a positive result[38, 39]. In a review by our research group regarding the effectiveness of LLLT in knee osteoarthritis, a significant dose-response relationship was discovered when the included trials were subgrouped using the WALT treatment recommendations for minimum dosage[40].

Furthermore, in a more recent placebo-controlled trial, we found some evidence that an upper limit for the effectiveness of LLLT exists in knee osteoarthritis[41]. These clinical observations are in line with the results of several in vivo and in vitro trials[42-45]. Whether such biphasic dose-response relationship exists in tendon disorders is unclear. Prior systematic reviews have investigated LLLT in Achilles tendinopathy or plantar fasciitis[12, 46-51]. Unfortunately, these reviews have one or more substantial limitations, such as a lack of a dose-response analysis[12], a lack of inclusion of trials reported in non-English languages[46-50], or the faulty use of a fixed effects meta-analysis model in the presence of highly heterogeneous studies[51]. Thus, the evidence regarding the effectiveness of LLLT on pain and disability in lower limb tendinopathy and plantar fasciitis is still somewhat unclear. Therefore, the objectives of the current review were to estimate the effectiveness of LLLT in tendinopathy and plantar fasciitis on patient-reported pain and disability using a dose-response analysis.

METHODS

This review was conducted in adherence to a prospectively registered PROSPERO protocol and is reported in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis statement 2009[52].

Literature search and selection of studies

We included randomised clinical trials in which the effectiveness of LLLT in tendon disorders of the lower extremity or plantar fasciitis was compared with sham (placebo) LLLT, other interventions or no intervention, in terms of self-reported pain and/or disability. There were no restrictions regarding publication date and language.

A search for eligible reports of trials were conducted in the databases PubMed, Embase and Physiotherapy Evidence Database (PEDro) on the 20th August 2020. Furthermore, references from relevant systematic reviews[47, 49, 51, 53, 54] and all the included trials were screened, and experts in the field were asked to provide additional published and unpublished trials. Abstracts were not included. The PubMed search string is included in the supplementary material.

Two independent reviewers (IFN and MBS) read the titles/abstracts of the publications identified by the search. Any article judged potentially eligible by a reviewer was retrieved in full text. The same two reviewers evaluated the full texts of all the potentially eligible articles and made a careful decision to include or exclude each article, with close attention to the eligibility criteria. Any article not fulfilling the eligibility criteria was excluded and had its details listed with reason for exclusion (supplementary material). Selection disagreements were resolved by discussion to consensus with the option of a third person's (JJ) final decision if necessary.

Risk-of-bias analysis

Two reviewers (IFN and MBS) independently assessed the risk-of-bias of the included trials with the 0-10 points PEDro scale[55]. This was done on outcome level, and since the outcomes of interest were patient-assessed pain and disability, the participants were considered the assessors. Therefore, the assessors can only be blinded in placebo-controlled trials. When risk-of-bias disagreements could not be resolved by discussion, a third reviewer (JJ) made the final consensus-based decision. The trials were labelled as being of 'high', 'moderate' or 'poor' methodological quality if they had a total PEDro score of ≥ 7, 5-6 or ≤ 4, respectively[56]. Risk of small study bias was assessed with a funnel plot and by comparing the difference between the point effect estimates from random and fixed effects meta-analyses.

Data-extraction and meta-analysis

Extraction of the following information was mandatory: number of participants allocated to laser and control groups, participant characteristics, type and duration of interventions, laser-specific application information (location of application, wavelength, energy density per treated spot, number of spots treated, mean power density per treated spot, treatment time per spot, treated area, laser sessions per week and total number of laser sessions, selected outcome measurement scales for data-extraction, time-points of assessments, effect estimates and adverse events.

The data collection was handled in a two-person procedure by IFN and MBS. One reviewer entered all the data in Excel sheets and the data were subsequently checked for correctness by another reviewer. If data-extraction disagreements could not be resolved by discussion, a third reviewer (JMB) made the final consensus-based decision.

All the meta-analyses were conducted using random effects models, weighting the individual trial results relatively even when statistical heterogeneity is present[57].

The pain results were synthesised using the Mean Difference (MD) method as this method allows for change and final scores to be combined[58]. Pain scores reported on the Visual Analogue Scale (VAS) and on the Numeric Rating Scale highly correlates[59] and were thus considered the same. Self-reported disability results were synthesised with the Standardised Mean Difference (SMD) method using change scores solely[58]. According to Cohen, a SMD of 0.2, 0.5 and 0.8 can be considered small, moderate and large, respectively [58].

Heterogeneity was measured using I^2-statistics (inconsistency)[60]. An inconsistency level of 25%, 50% and 75% would be considered low, moderate and high, respectively[61]. Standard deviations (SD) for meta-analysis were extracted or estimated from other variance data in the following prioritised order: SD, standard error, 95 % confidence interval, p-value, interquartile range, median of correlations, visually from graph, correlation of 0.6 or mean of SDs from similar trials.

Trials were subgrouped by laser dose using the WALT treatment recommendations[62, 63], as specified in the a priori protocol. WALT recommends irradiating minimum of 2-3 points on the tendon or fascia. In Achilles and patellar tendinopathy, the recommended dose with 904 nm wavelength laser is minimum 2 joules per point. When utilizing 780-860 nm wavelength laser, the minimum dose is 4 Joules per point. In plantar fasciitis, the recommended minimum dose is 2 joules per point with a 904 nm wavelength laser or 4 joules per point with 780-860 nm wavelength laser. We subgrouped the trials as recommended dose and non-recommended laser dose. If the trial reports lacked sufficient dose parameters to be identified as recommended or non-recommended dose, they were categorised as unclear laser dose.

Two time-points of assessment were selected for analysis, that is, immediately after the end of LLLT and last time-point of assessment 2-14 weeks after completed LLLT (follow-up).

IFN and MBS performed the meta-analyses, using Excel 2016 (Microsoft) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Patient and public involvement

Patients or the public were not involved in the conceptualization or carrying out of this research.

RESULTS

A total of 870 records were identified in the search, of which 18 reports of trials (n = 784) were included in review and meta-analysis (Figure 1 and Table 1). LLLT was applied to participants with patellar tendinopathy in two trials, Achilles tendinopathy in five trials and plantar fasciitis in 11 trials. LLLT was compared with placebo in 10 trials, other interventions in five trials and as an adjunct intervention in three trials. Two trials were reported in non-English language, and one trial

was unpublished (Naterstad et al.). The excluded articles were listed with reasons for omission (supplementary material). The mean age of the participants was 43.6 (minimum <18, maximum 54.5, data from 14 trials), and the mean baseline pain intensity was 64.2 mm on the VAS (minimum 19.3 mm, maximum 85 mm, data from 18 trials). No adverse events were reported by any of the trial authors. None of the trial authors declared that they had received funding from the laser industry.

Table 1 Characteristics of the included trials

First author, year	Participants at baseline (intervention)*	Participants at baseline (control)*	Intervention versus control	Outcome and time of reassessment after baseline (time used for analysis in bold)
Patellar tendinopathy				
Liu 2014**[64]**, LLLT versus ET	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 67.9±13.2	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 65.7±15.4	4 weeks of LLLT versus 4 weeks of eccentric ET	Pain: VAS Disability: Modified-VISA Reassessment: **4** weeks
Liu 2014**[64]**, LLLT+ET versus ET	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 67.9±12.2	n: 7 Age years: ≥ 18, ≤ 23 VAS pain mm: 65.71±15.4	4 weeks of LLLT and eccentric exercise therapy versus 4 weeks of eccentric ET	Pain: VAS Disability: Modified-VISA Reassessment: **4** weeks
Stergioulas 2003**[65]**	n: 23 Age years: 29.2±13.4 VAS pain mm: 81.7±13.4	n: 21 Age years: 29.8±13.8 VAS pain mm: 75.9±18.8	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS Disability: Functional Index Questionnaire Reassessment: **2** and **6** weeks
Achilles tendinopathy				
Darre 1994**[66]**	n: 46 Age years: ≥ 18 VAS pain mm: 58.5±37.9	n: 43 Age years: ≥ 18 VAS pain mm: 72±34.3	2.4 weeks of LLLT versus 2.4 weeks of sham LLLT	Pain: VAS Disability: - Reassessment: **2.4** weeks
Naterstad**	n: 20 Age years: 45.4±14.7 VAS pain mm: 52.9±26.1	n: 21 Age years: 45.8±13.9 VAS pain mm: 53.8±26.7	4 weeks of LLLT and cryotherapy and 12 weeks of eccentric and concentric ET versus 4 weeks of sham LLLT and cryotherapy and 2 weeks of eccentric and concentric ET	Pain: THIP VAS most painful activity Disability: THIP VAS ADL Reassessment: **4** and **12** weeks
Stergioulas 2008**[67]**	n: 20 Age years: 30.1±4.8 VAS pain mm: 79.8±9.5	n: 20 Age years: 28.8±4.8 VAS pain mm: 81.8±11.6	8 weeks of LLLT and eccentric ET versus 8 weeks of sham LLLT and eccentric ET	Pain: VAS during activity Disability: - Reassessment: 4, **8** and **12** weeks
Tumilty 2008**[68]**	n: 10 Age years: 41.4±7.6 VAS pain mm: 47.8±25.9	n: 10 Age years: 42.5±8.5 VAS pain mm: 39±20.2	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: VAS in morning Disability: - Reassessment: **4** and **12** weeks
Tumilty 2012**[69]**	n: 20 Age years: 45.6±9.1 NRS pain mm: 21.1±1.17	n: 20 Age years: 46.5±6.4 NRS pain mm: 19.3±0.94	4 weeks of LLLT and 12 weeks of eccentric ET versus 4 weeks of sham LLLT and 12 weeks of eccentric ET	Pain: NRS Disability: - Reassessment: **4**, **12** and 52 weeks
Plantar fasciitis				
Basford 1998**[70]**	n: 16 Age years: 42.5 (26-64)* VAS pain mm: 57.9 (22.2-97)*	n: 15 Age years: 42 (33-51)* VAS pain mm: 46.6 (4-86)* (	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: Pain when walking in morning Disability: Limping in morning Reassessment: 2, **4** and **8** weeks

Cinar 2017**[71]**	n: 29 Age years: 46.59±10.1 VAS pain mm: 61.3±19.4	n: 22 Age years: 44.18±9.7 VAS pain mm: 54.9±19.7	3 weeks of LLLT and stretching versus 3 weeks of stretching	Pain: VAS Disability: AOFAS-F activity limitations Reassessment: **3** and **12** weeks
Cinar 2018**[72]**	n: 24 Age years: 46.5±10.3 NRS pain mm: 6.3±1.42	n: 17 Age years: 44±8.6 NRS pain mm: 6.2±2.14	3 weeks of LLLT and 12 weeks of stretching versus 12 weeks of stretching	Pain: NRS Disability: - Reassessment: **3** and **12** weeks
Cinar 2018**[72]**, ESWT	n: 24 Age years: 46.5±10.3 NRS pain mm: 6.3±1.42	n: 25 Age years: 45.4±9.7 NRS pain mm: 6.7±2.67	3 weeks of LLLT and 12 weeks of stretching versus 3 weeks of ESWT (2000 mJ/mm^2, session once per week) and 12 weeks of stretching	Pain: NRS Disability: - Reassessment: **3** and **12** weeks
Elsehrawy 2018**[73]**	n: 23 Age years: 46.4±10 VAS pain: 85±8	n:23 Age years: 46±10.2 VAS pain: 82±15	3 weeks of LLLT versus 2 weeks of ESWT (2050 shocks/min, 10 Hz, 2.5 bars once per week)	Pain: VAS Disability: FFI disability subscale Reassessment: **4** weeks
Kiritsi 2010**[74]**	n: 15 Age years: 41±12 VAS pain mm: 67±8.3	n: 15 Age years: 41±12 VAS pain mm: 67±9.3	6 weeks of LLLT versus 6 weeks of sham LLLT	Pain: ADL VAS Disability: - Reassessment: **6** weeks
Koteeswaran 2020**[75]**	n: 15 Age years: 30-60 NRS pain: 74.7±11.9	n: 15 Age years: 30-60 NRS pain: 72.7±8	2 weeks of LLLT and stretching versus 2 weeks of TUS and stretching	Pain: NRS Disability: FAAM Reassessment: **2** weeks
Lamba 2013**[76]**	n: 40 Age years: 40.9±10.4 VAS pain mm: 57.5±10.8	n: 40 Age years: 40.4±9.7 VAS pain mm: 62±7.6	4 weeks of LLLT and stretching versus 4 weeks of sham LLLT and stretching	Pain: VAS Disability: - Reassessment: 1,2, 3 and **4** weeks
Macias 2015**[77]**	n: 37 Age years: ≥ 18 VAS pain mm: 69.1±12.7	n: 32 Age years: ≥ 18 VAS pain mm: 67.6±11.8	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: VAS heel pain Disability: FFI disability subscale **8** weeks Reassessment: 1, 2, **3**, 6 and **8** weeks
Sanmak 2019**[78]**	n: 17 Age years: 53* VAS pain mm: 70*	n: 17 Age years: 49* VAS pain mm: 80*	4 weeks of LLLT versus 3 weeks of ESWT (2 bar with 2,000 shocks/min at 10 Hz once per week)	Pain: VAS Reassessment: **4** and **8** weeks
Ulusoy 2017**[79]**, TUS	n: 20 Age years: 53.4 VAS pain mm: 68.7	n: 20 Age years: 50.95 VAS pain mm: 66.6	3 weeks of LLLT versus 3 weeks of TUS (1 mHz; 2 W/cm2)	Pain: VAS in morning Disability: - Reassessment: **7** weeks
Ulusoy 2017**[79]**, ESWT	n: 20 Age years: 53.4±14.7 VAS pain mm: 68.7±12.5	n: 20 Age years: 54.4±6.9 VAS pain mm: 66±11.2	3 weeks of LLLT versus 3 weeks of ESWT (2.5 bar with 2,000 shocks/min at 10 Hz three times per week)	Pain: VAS in morning Disability: - Reassessment: **7** weeks
Yüzer 2006**[80]**	n: 24 Age years: 49.6±1.2 VAS pain mm: 80±12	n: 30 Age years: 51.5±11.5 VAS pain mm: 76±15	1.4 weeks of LLLT versus steroid injection	Pain: VAS Disability: - Reassessment: **5.4**, **13.4** and 25.4 weeks

Numbers for age and pain are means ± standard deviations, unless otherwise indicated. *Median with or without interquartile range.
** Naterstad et al. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial
ADL, activity of daily living; AOFAS-F, American Orthopedic Foot and Ankle Score Function; ESWT, Extracorporeal Shockwave Therapy; ET, exercise therapy; FAAM, Foot and ankle ability measurement questionnaire; FFI, Foot Function Index; LLLT, Low-Level Laser Therapy; NRS, Numeric Rating Scale; THIP, Tendinopathy Health Impact Profile; TUS, therapeutic ultrasound; VAS, Visual Analogue Scale.

LLLT was compared with placebo LLLT in 10 trials[65, 66, 68-70, 74, 76, 77, 81], and exercise therapy or stretching exercises was applied as a co-intervention in five of these trials. LLLT was compared with exercise therapy or stretching exercises in three trials[64, 71, 72]. A comparison between LLLT and Extracorporeal Shockwave Therapy (ESWT) in plantar fasciitis was performed in four trials[72, 73, 78, 79]. LLLT was compared to therapeutic ultrasound in two trials[75, 79], and LLLT was compared to steroid injection in one trial[80]. Recommended laser doses were applied in at least 11 trials[64-68, 71, 72, 74, 76, 79] and a non-recommended dose was used in at least one trial[69]. We were unable to categorise the laser doses in the remaining six trials[70, 73, 75, 77, 78, 80] due to inadequately or missing descriptions of laser parameters (Table 2). Two different LLLT doses were applied in the same session in two of the trials [64, 74].

Table 2 LLLT characteristics of the included trials

First author, year	Wave-length (nm)	Mean output power (mW)	Seconds per treatment spot (s)	Joules per treatment spot (J)	Number of spots treated	Number of sessions/Weeks	Dose recommended by WALT
Patellar tendinopathy							
Liu 2014**[64]**	810	200	600	-	1×	24/4	Yes
	810	200	300	-	2		
Stergioulas 2003**[65]**	904	50	300	1.2	10	10/2	Yes
Achilles tendinopathy							
Darre 1994**[66]**	830	30	-	4	4	12/2.5	Yes
Naterstad**	904	60	50	3	6	12/4	Yes
Stergioulas 2008**[67]**	820	30	-	0.9	6	12/8	Yes
Tumilty 2008**[68]**	810	100	30	3	6	12/4	Yes
Tumilty 2012**[69]**	810	7	30	0.21	6	12/4	No
Plantar fasciitis							
Basford 1998**[70]**	830	30	-	-	3 *	12/4	Unclear
Cinar 2017**[71]**	830	100	80	5.6	5	10/3	Yes
Cinar 2018**[72]**	830	100	80	5.6	5	10/3	Yes
Elsehrawy 2018**[73]**	830	-	-	-	3 *	6/3	Unclear
Kiritsi 2010**[74]**	904	60	-	8.4	1×	18/6	Yes
	904	60	-	-	2 *		
Koteeswaran 2020**[75]**	830	-	180	-	3	9/3	Unclear
Lamba 2013**[76]**	820	100	80	-	3 *	12/4	Yes
Macias 2015**[77]**	635	17	600	-	3	6/3	Unclear
Sanmak 2019**[78]**	685	30	60	-	2 *	12/4	Unclear
Ulusoy 2017**[79]**	830	50	200	-	3 *	15/3	Yes
Yüzer 2006**[80]**	904	-	30	-	-	10/1.4	Unclear

× Two different dosages applied within the same session.
*One or more spots/areas treated with movement of the laser probe.
**Naterstad et al. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial
LLLT, Low-Level Laser Therapy; WALT, World Association for Laser Therapy.

Overall pain and disability results pain and disability - LLLT versus any control

Data allowing for a meta-analysis of an immediate pain change were available from 16 trials with recommended, non-recommended or unknown laser dosing.

Overall, pain was significantly reduced by LLLT over any control immediately after completed therapy (13.15 mm VAS (95% CI: 7.82 to 18.48), I^2 = 65%, n = 784) (Figure 2) and at follow-ups 4-12 weeks later (12.56 mm VAS (95% CI: 5.69 to 19.42), I^2 = 48%, n = 556) (Figure 3).

Overall, the disability results immediately after completed therapy significantly favoured LLLT over any control (SMD = 0.39 (95% CI: 0.09 to 0.7), I^2 = 30%, n = 260) (Figure 4). A disability reduction by LLLT remained significant at follow-ups 4-9 weeks after completed therapy (SMD = 0.32 (95% CI: 0.05 to 0.59), I^2 = 4%, n = 222) (Figure 5).*Overall and subgroup pain results - LLLT versus placebo-control*

Overall, pain was significantly reduced by LLLT over placebo-control immediately after completed therapy (11.48 mm VAS (95% CI: 2.68 to 20.28), I^2 = 73%, n = 507) (Figure 6) and during follow-ups 4-8 weeks after completed therapy (13.62 mm VAS (95% CI: 2.18 to 25.06), I^2 = 68%, n = 277) (Figure 3).

The recommended laser doses significantly reduced pain compared with placebo immediately after completed therapy (14.98 mm VAS (95% CI: 3.74 to 26.22), I^2 = 67%, n = 367) (Figure 6). A non-recommended laser dose from a single trial provided no significant pain reduction immediately after completed therapy (-3.0 mm VAS (95% CI: -11.17 to 5.7), n = 40) (Figure 6). Trials with unknown laser doses significantly favoured LLLT over placebo-control immediately after completed therapy (10.83 mm VAS (95% CI: 2.44 to 19.21), I^2 = 0%, n = 100). The between-subgroup difference was significant (p = 0.02) (Figure 6).

At follow-ups 4-8 weeks after completed therapy, the recommended laser doses significantly reduced pain compared with placebo (14.00 mm VAS (95% CI: 2.81 to 25.19), I^2 = 5%, n = 136) (Figure S1, supplementary material). A non-recommended dose provided in a single trial did not significantly reduce pain compared with placebo at follow-up 8 weeks after completed therapy (0.0 mm VAS (95% CI: -7.62 to 7.62), n = 40) (Figure S1, supplementary material). At follow-ups 4-5 weeks after completed therapy, trials with unknown laser doses demonstrated a significant pain reduction by LLLT compared with placebo (23.94 mm VAS (95% CI: 14.39 to 33.48), I^2 = 0%, n = 97) (Figure S1, supplementary material). The between-subgroup difference was significant (p < 0.001) (Figure S1, supplementary material).*Subgroup pain results - LLLT versus no intervention*
Pain was significantly lowered by the recommended laser doses when used as an adjunct to exercise, stretching and insoles over exercise, stretching and insoles alone, both immediately after completed therapy (18.15 mm VAS (95% CI: 10.55 to 25.76), I^2 = 0%, n = 104) (Figure S2, supplementary material) and at follow-up 9 weeks after completed therapy (19.67 mm VAS (95% CI: 5.16 to 34.18), I^2 = 0%, n = 80) (Figure S3, supplementary material).

Overall and subgroup pain results - LLLT versus other interventions
Overall, pain was significantly reduced by LLLT compared with other interventions immediately after completed therapy (13.23 mm VAS (95% CI: 4.07 to 22.39), I^2 = 66%, n = 173) (Figure S4, supplementary material). Follow-up results of pain 4-12 weeks after completed therapy favoured LLLT over other interventions, but not significantly (9.41 mm VAS (95% CI: -0.44 to 19.26), I^2 = 16%, n = 193) (Figure S5, supplementary material).

The recommended laser doses were compared with exercise therapy in one trial and ESWT in another trial immediately after completed therapy and the pain results favoured LLLT, but not significantly (13.91 mm VAS (95% CI: -1.34 to 29.15), I^2 = 65%, n = 63) (Figure S4, supplementary material).

The pain results from three trials with unknown laser doses, in which two groups received ESWT and one group received therapeutic ultrasound, favoured LLLT immediately after completed therapy, but not significantly (12.88 mm VAS (95% CI: -1.29 to 27.04), I^2 = 77%, n = 110) (Figure S4, supplementary material).
At follow-ups 4-12 weeks after completed therapy, pain was significantly lowered by the recommended laser doses compared with other interventions (15.90 mm VAS (95% CI: 2.30 to 29.51), I^2 = 0%, n = 103) (Figure S5, supplementary material). Pain was not significantly lowered by unknown laser doses compared with other interventions at follow-ups 4-12 weeks after completed therapy (2.93 mm VAS (95% CI: -15.8 to 21.67), I^2 = 52%, n = 87) (Figure S5, supplementary material).

Overall and subgroup disability results - LLLT versus placebo-control

Overall, the disability results favoured LLLT over placebo-control immediately after completed therapy, but not significantly (SMD = 0.2 (95% CI: -0.18 to 0.58), I^2 = 0%, n = 107) (Figure 4). The same applied to the follow-up results 4-8 weeks after completed therapy (SMD = 0.19 (95% CI: -0.11 to 0.49), I^2 = 0%, n = 173) (Figure S6, supplementary material).

The disability results immediately after completed therapy favoured the recommended laser doses over other interventions, but not significantly (SMD = 0.25 (95% CI: -0.21 to 0.7), I^2 = 0%, n = 76) (Figure S7, supplementary material). The same applied to unknown laser doses compared with placebo-control immediately after completed therapy (SMD = 0.10 (95% CI: -0.61 to 0.8), n = 31) (Figure S7, supplementary material).

At follow-ups 4-8 weeks after completed therapy, the disability results favoured the recommended laser doses over other interventions, but not significantly (SMD = 0.24 (95% CI: -0.21 to 0.7), I^2 = 0%, n = 76) (Figure S6, supplementary material). The same applied to the unknown laser doses compared with placebo-control immediately after completed therapy (SMD = 0.14 (95% CI: -0.26 to 0.54), I^2 = 0%, n = 107) (Figure S6, supplementary material).

Overall and subgroup disability results - LLLT versus other interventions

The overall disability results immediately after completed therapy favoured LLLT, but not significantly (SMD = 0.58 (95% CI: -0.11 to 1.27), I^2 = 56%, n = 90) (Figure 4).

The recommended laser doses neither provided a significant disability reduction compared with other interventions immediately after completed therapy (SMD = 0.2 (95% CI: -0.85 to 1.25), n = 14) (Figure S8, supplementary material). The same applied to unknown laser doses compared with other interventions immediately after completed therapy (SMD = 0.73 (95% CI: -0.26 to 1.72), n = 76) (Figure S8, supplementary material).

Subgroup disability results - LLLT versus no intervention

The disability results of the recommended laser doses applied as an adjunct to exercise therapy or stretching immediately after completed therapy favoured LLLT, but not significantly (SMD = 0.68 (95% CI: -0.49 to 1.85), I^2 = 69%, n = 61) (Figure S9, supplementary material). At follow-up 9 weeks after completed therapy, disability was significantly lowered by the recommended laser doses as an adjunct to stretching and insoles compared with exercise therapy and insoles alone (SMD = 0.82 (95% CI: 0.24 to 1.41), n = 49) (Figure S10, supplementary material).

Sensitivity analysis of laser dose categorisation

The irradiation procedure by Darre et al.[66] was judged as a recommended laser dose, based on the reported dose parameters in the paper. However, the dose description is somewhat sparse and could be misinterpreted. If the study by Darre et al. was allocated to the unknown laser dose subgroup, the statistical heterogeneity would be eliminated in the recommended laser dose group and the estimated pain reduction would be increased to 21.12 mm VAS ((95% CI: 14.94 to 27.31), I^2 = 0%, n = 278) versus placebo immediately after completed therapy (Figure S11, supplementary material).

Risk-of-bias within studies

Ten of the included trials were found to be of high methodological quality, and the remaining eight included trials were found to be of moderate methodological quality (Table 3). All the trials featured adequate randomisation. Allocation concealment was sufficient in 11 (61%) of the trials. The groups were similar at baseline in 15 (83%) of the trials. The participants were blinded in nine (50%) of the trials. The therapists were blinded in five (28%) of the trials, all of which were placebo-controlled. The assessors were blinded in seven (39%) of the trials, all of which were placebo-controlled. Outcome data were available from more than 85% of the participants in 14

(78%) of the trials. An intention-to-treat analysis was used in 10 (56%) of the trials. A between-group statistical comparison was performed in all the trials. Point measures and variability outcome data were stated in 17 (94%) of the trial reports.

The lack of therapist and assessor blinding were the two most obvious methodological inadequacies. However, risk-of-bias subgroup analyses performed post-hoc revealed that there was no significant interaction between the effect estimates and the lack of blinding (Figures S12 and S13, supplementary material).

Risk-of-bias across studies (small study bias)

In a random effects model, small and large trials are weighted relatively even when statistical heterogeneity is present. In a fixed effects model, the heterogeneity is ignored and will not influence the weights. Smaller studies in meta-analyses tend to show more positive results than larger trials[82]. However, there was almost no difference between the pain results of the two meta-analysis models, indicating that no small study bias exists (Figures S14 and S15, supplementary material). Likewise, there was no obvious asymmetry in a funnel plot based on the same meta-analyses of pain, indicating that no small study bias was present (Figure S16, supplementary material).

Table 3 PEDro score

Study ID	**Item number**											**Total**	**Quality**
	1*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Basford 1998[70]	+	+	-	+	+	-	+	+	-	+	+	7	High
Cinar 2017[71]	+	+	+	+	-	-	-	+	+	+	+	7	High
Cinar 2018[72]	+	+	+	+	-	-	-	+	+	+	+	7	High
Darre 1994[66]	+	+	+	-	+	+	-	-	-	+	-	5	Moderate
Elsehrawy 2018[73]	+	+	-	+	-	-	-	+	-	+	+	5	Moderate
Kiritsi 2010[74]	+	+	+	+	+	+	+	-	-	+	+	8	High
Koteeswaran 2020[75]	+	+	-	+	-	-	-	+	+	+	+	6	Moderate
Lamba 2013[76]	+	+	-	+	+	-	-	+	-	+	+	6	Moderate
Liu 2014[64]	+	+	-	+	-	-	-	+	+	+	+	6	Moderate
Macias 2015[77]	+	+	+	+	+	-	+	+	+	+	+	9	High
Naterstad	+	+	+	+	+	+	+	+	+	+	+	10	High
Sanmak 2019[78]	+	+	+	+	-	-	-	+	+	+	+	7	High
Stergioulas 2003[65]	+	+	-	+	+	-	+	-	-	+	+	6	Moderate

Stergioulas 2008[67]	+	+	+	+	+	-	-	-	+	+	+	8	High
Tumilty 2008[68]	+	+	+	+	+	+	+	+	+	+	+	10	High
Tumilty 2012[69]	+	+	+	+	+	+	+	+	+	+	+	10	High
Ulusoy 2017[79]	+	+	-	+	-	-	-	+	-	+	+	5	Moderate
Yüzer 2006[80]	+	+	+	+	-	-	-	-	-	+	+	5	Moderate

*Item not included in the mean score.
** Naterstad et al. Efficacy of Low-level Laser Therapy as an addition to exercise and cryotherapy in chronic Achilles tendinopathy: a double-blinded randomised controlled trial
PEDro, Physiotherapy Evidence Database.
1. Eligibility criteria specified.
2. Random allocation.
3. Concealed allocation.
4. Groups similar at baseline.
5. Subject blinding.
6. Therapist blinding.
7. Assessor blinding.
8. Less than 15% dropout.
9. Intention-to-treat analysis.
10. Between-group statistical comparisons.
11. Point measures and variability data.

DISCUSSION

We investigated the effectiveness of LLLT in tendon and aponeurosis disorders of the lower extremity. Our overall meta-analysis results demonstrated that pain and disability were statistically significantly reduced by LLLT compared with any control both immediately after completed therapy and in the follow-up period, that is, 4-12 weeks after completed therapy for pain and 4-8 weeks after completed therapy for disability.

Like in our previous meta-analysis of LLLT in knee osteoarthritis[40], we sub-grouped the included trials in the current review using the WALT treatment recommendations.[62, 63] Compared with placebo-control, the recommended laser doses in the current review generally had a larger pain-relieving effect than non-recommended laser both immediately after therapy and in the follow-up period. Similarly, the recommended laser doses had a significant pain-relieving effect as an adjunct to exercise therapy, stretching and insoles both immediately after completed therapy and in the follow-up period. Compared with other treatment modalities, the recommended laser doses were significantly superior, but only at follow-up and only as a pain treatment.

The minimal clinically important improvement (MCII) for pain expressed on the VAS or NRS has not been established for tendinopathy in the lower extremity[83], even though pain is a prominent feature of this condition. In plantar fasciitis, the MCII for VAS pain has been estimated to be 8 mm for average pain[84], and our results are above this threshold in all comparisons.

As for disability, we found that LLLT overall had a small and significant effect both immediately after completed therapy and in the follow-up period. Compared with placebo, there were no significant effect of LLLT on disability immediately after completed therapy and at follow-ups. Only Cinar et al.[71] provided follow-up data on disability regarding LLLT as an add-on to exercise therapy. They found a large and significant positive effect on disability 12 weeks after

completed therapy, however, their results are based only on 49 participants[71], and thus this meta-analysis result should be interpreted with caution.

We were unable to dose categorise the study by Macias et al.[77], since they used a laser within the visible spectrum (635 nm), which is not mentioned in the WALT treatment guidelines. Light in the red wavelengths (600-700 nm) penetrates the tissue to a lesser extent than light with a wavelength of 700-1000 nm[85]. Macias et al. utilized a relatively low mean output power, but they stated that they irradiated the tissue for 600 seconds and achieved a significant pain reduction. The methodological quality of their trial[77] was categorised as high, with a PEDro score of 9.

Sanmak et al.[78] also used a laser within the red spectrum, but they applied a much smaller dose. Sanmak et al.[78] compared LLLT with ESWT in plantar fasciitis and found no difference between the groups regarding pain immediately after treatment, but an insignificant better result for ESWT 4 weeks after completed treatment. Comparing LLLT to ESWT, we would expect different effect-time profiles for pain alleviation, as the effect of ESWT might be greater at later time-points[86]. Sanmak et al.[78] applied LLLT in a circular motion on the insertion site of the plantar fascia for 60 seconds and along the fascia for another 60 seconds. They stated that they irradiated the tissue with 2 J/cm^2, which according to our calculation (Watt*seconds) corresponds to a relatively low mean output power of 18 mW/cm^2. Moving the laser probe during irradiation will yield a smaller laser dose per treated cm^2, and larger movement will for instance reduce the energy delivered per treated cm^2. Additionally, the skin underneath the heel is thick[87], and thus absorbs a large percentage of the laser.

We did not identify any trials focusing on trochanter tendinopathy, peroneal or tibialis posterior tendinopathy. In a double-blinded randomised trial by Lögdberg-Andersson et al.[88], the effect of a 904 nm wavelength laser in participants with trochanteritis or myofascial pain was investigated. They found a significant positive effect compared with placebo on pain expressed on a VAS and with algometry, both at the end of treatment and four weeks after[88]. This trial was not included in our review, since we were unable to isolate the participants of interest.

We were only able to identify two randomised controlled trials regarding the effect of LLLT compared with a control in patellar tendinopathy. Ashok et al.[89] have compared the effect of LLLT to that of therapeutic ultrasound in persons with patellar tendinopathy, and they found a statistically significant effect in favour of LLLT , both on pain reduction and function. However, it should be noted that this trial is small (n = 8) and only of moderate methodological quality. Another LLLT trial by Meier et al.[90] included participants with both patellar tendinopathy (n = 58) and Achilles tendinopathy (n = 52). We omitted this trial, since it solely concerned the effects of an invisible (904 nm wavelength) laser versus a red (632 nm wavelength) laser. Meier et al.[90] stated that the red laser was placebo, but the laser dose applied in the sham procedure may possibly have had a photochemical effect. Both groups achieved a positive effect on a combined index of pain and function, favouring the 904 nm wavelength laser, but the report of the trial neither includes point effect estimates, nor variability data.

The presence and role of inflammation in chronic tendinopathy has been an ongoing debate in the last few decades. There is currently increased support that inflammation has a causal role in tendinopathy, where immune cells and molecular mediators are included as inflammatory components[91-93]. PGE_2 has been suggested to sustain inflammation and pain in human tendon disease[94]. In Achilles tendinopathy, a reduction of PGE_2 and a concurrent increased pain pressure threshold after LLLT were found in a double-blinded randomised clinical trial by Bjordal et al.[95], where microdialysis of the tendon was performed in seven participants. The participants had aggravated the symptoms through a pain inducing activity immediately prior to the examination. Only the immediate (105 minutes) response to LLLT was investigated in the trial, but the findings support the notion that LLLT may have an anti-inflammatory effect in Achilles tendinopathy.

Several authors of the included trials failed to adequately describe the laser dose parameters used. A LLLT dose-response relationship has been established in systematic reviews of tendinopathy[35-37] and osteoarthritis[40]. In the current review, some of the statistical heterogeneity is plausibly due to the variation in laser doses applied. The statistical heterogeneity of the dose subgroup analyses was generally lower than in the overall (any dose) analyses and this indicates that the laser dose might be more important for the effect than the location of the tendinopathy. The only study that caused noteworthy statistical heterogeneity in the dose subgroup analysis with placebo-control was the one by Darre et al.[66]. Most of the pain and disability analyses comparing LLLT with other interventions were based on trials of plantar fasciitis. These analyses yielded a moderate level of statistical heterogeneity, and it may be explained by the variation in control interventions.

The included trials had a moderate to high methodological quality (mean PEDro score = 7.1). Although therapist and assessor blinding lacked in many of the included studies, the lack of blinding was not significantly associated with higher effect estimates (supplementary material).

Future trials on the topic should include larger patient samples and directly compare the effectiveness of different LLLT parameters. Additionally, systematic reviews of LLLT should include dose-response investigations.

Strengths and limitations of this study

This review was conducted in conformance with a detailed a priori published protocol, which includes, for example, a plan for subgrouping the trials by laser dose. The review includes results from two studies reported in non-English language[66, 80] and an unpublished study. The review features meta-analyses with direct comparisons between LLLT and placebo LLLT, other interventions and no intervention. Although only one reviewer extracted data from the included trials, the extracted data was checked for correctness by another reviewer.

Implications for practice

The LLLT dose parameters were inadequately described in six (35%) of the trial articles. This prohibited a comprehensive laser dose-response relationship investigation using the WALT treatment recommendations.[38, 39] Since the laser doses identified as WALT recommended doses provided significantly positive results in most instances, we suggest adhering to these recommendations until further trials increase the precision of the analysis.

CONCLUSIONS

LLLT significantly reduces pain and disability in lower extremity tendinopathy and plantar fasciitis in the short and medium term. Long-term data was not available. Some uncertainty about the effect size remains due to wide confidence intervals and lack of larger trials.

Author contributions IFN and MBS wrote the PROSPERO protocol. IFN and MBS selected the trials, with the involvement of JJ when necessary. IFN and MBS judged the risk-of-bias, with the involvement of JJ when necessary. IFN and MBS extracted the data. IFN and MBS translated the non-English articles. IFN performed the analyses, under supervision by MBS. IFN, JJ, JMB, CC, RABLM and MBS participated in interpreting of the results. IFN drafted the first version of the manuscript, and subsequently revised it, based on comments by JJ, JMB, CC, RABLM and MBS. All authors read and accepted the final version of the manuscript.

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access to all data in the study and had the final responsibility for the decision to submit for publication.

Competing interests JMB and RABLM are former board members and prior presidents of the World Association for Laser Therapy, a non-profit research organization from which they have never received funding, grants or fees. The other authors declared that they had no conflict of interests related to this work.

Patient consent for publication Not required.

Ethical approval Not required.

Data availability statement The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Legends:

Figure 1 Flow chart illustrating the trial identification process
PEDro, Physiotherapy Evidence Database.

Figure 2 Overall pain results immediately after completed therapy - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure 3 Overall pain results at follow-ups - LLLT versus any control
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure 4 Overall disability results immediately after completed therapy - LLLT versus any control

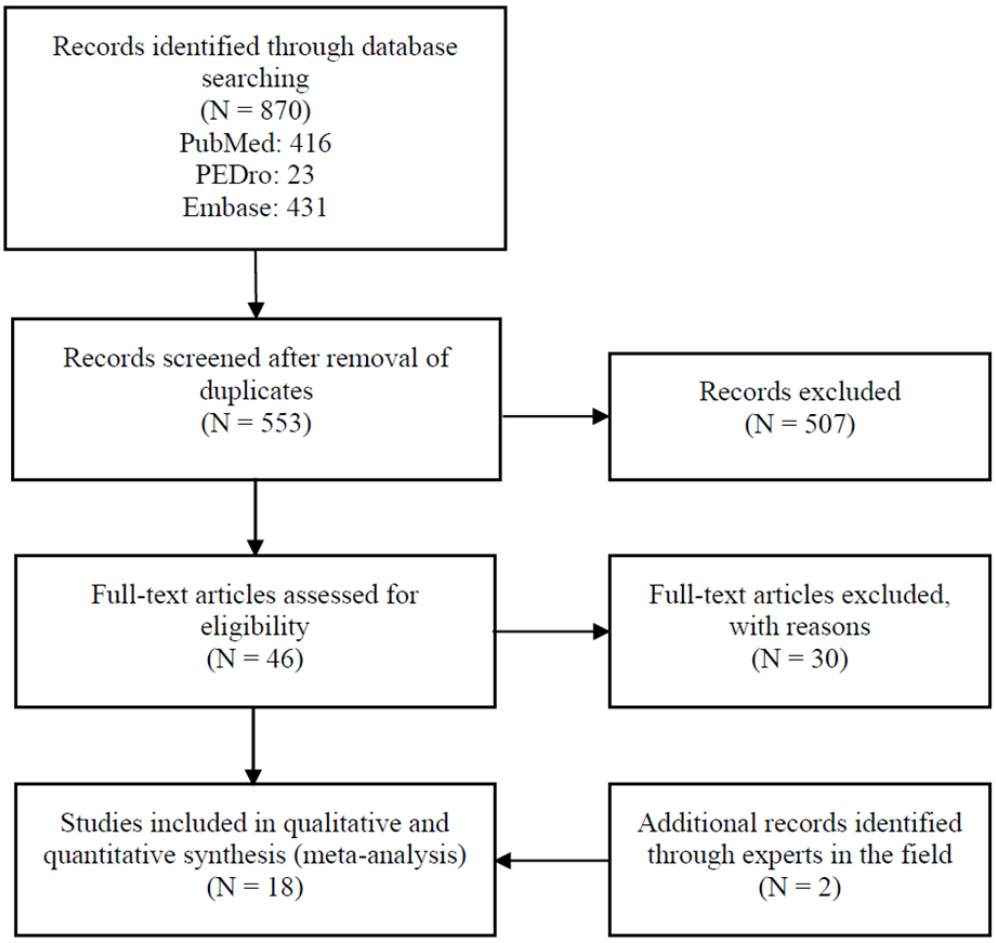
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S = stretching; TU, Therapeutic Ultrasound.

Figure 5 Overall disability results at follow-ups - LLLT versus any control

AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Figure 6 Subgroup pain results immediately after completed therapy - LLLT versus placebo-control

AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.



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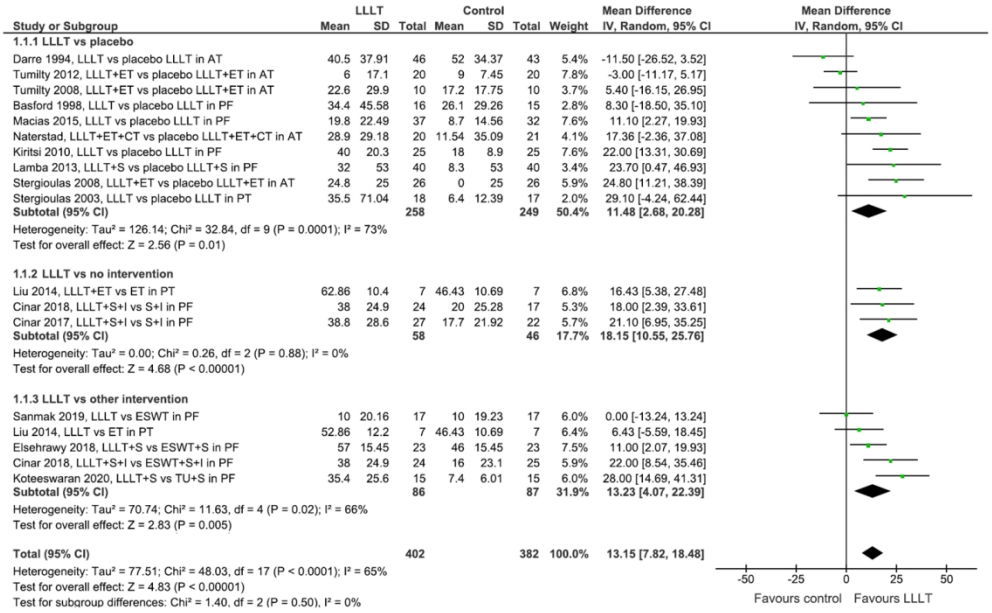

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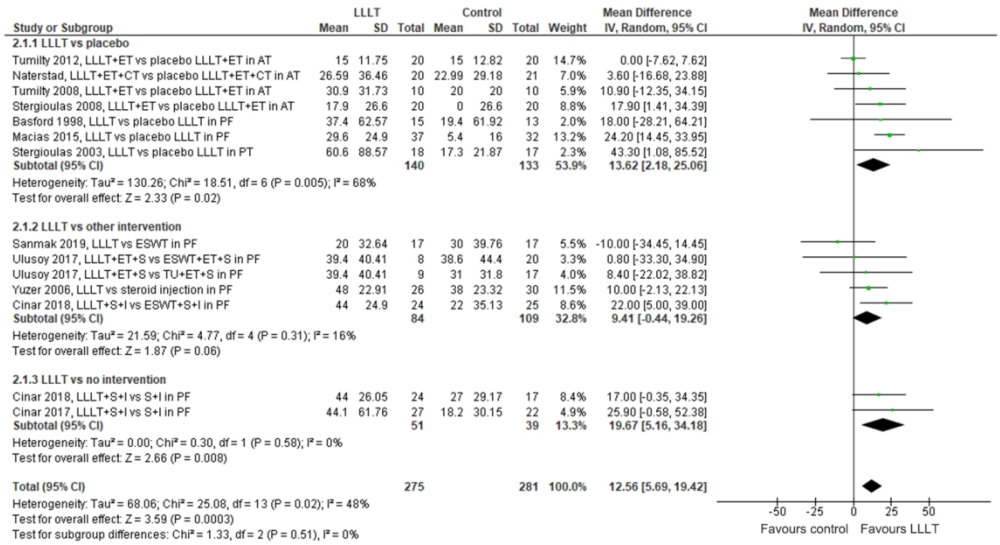

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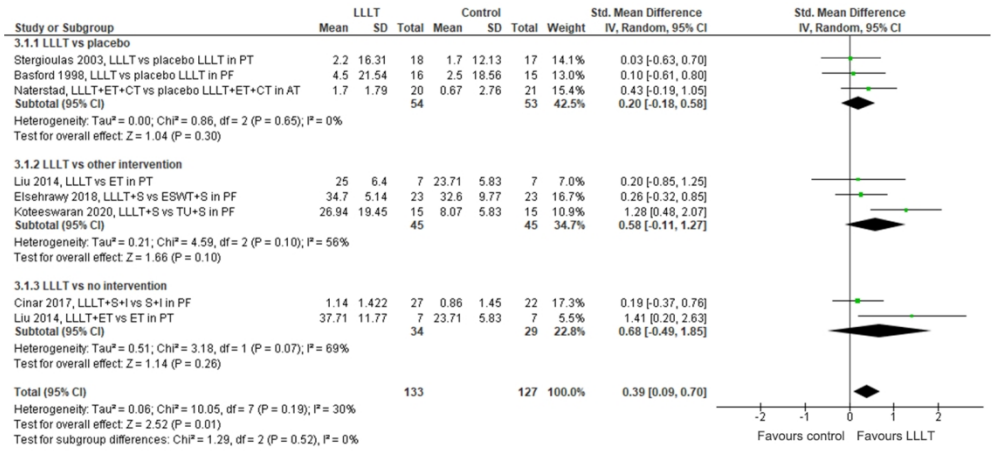

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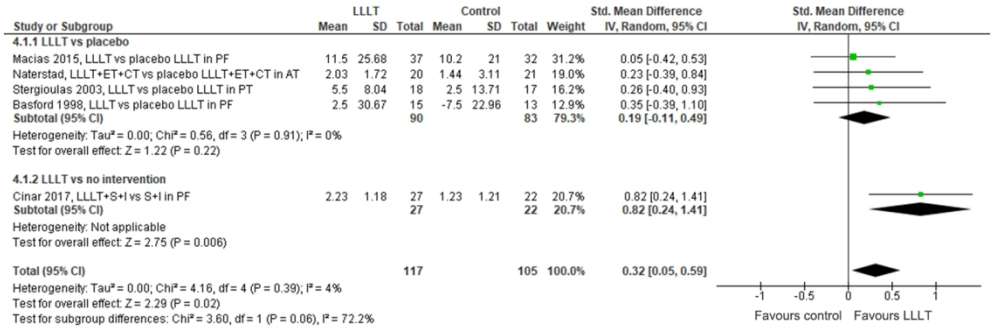

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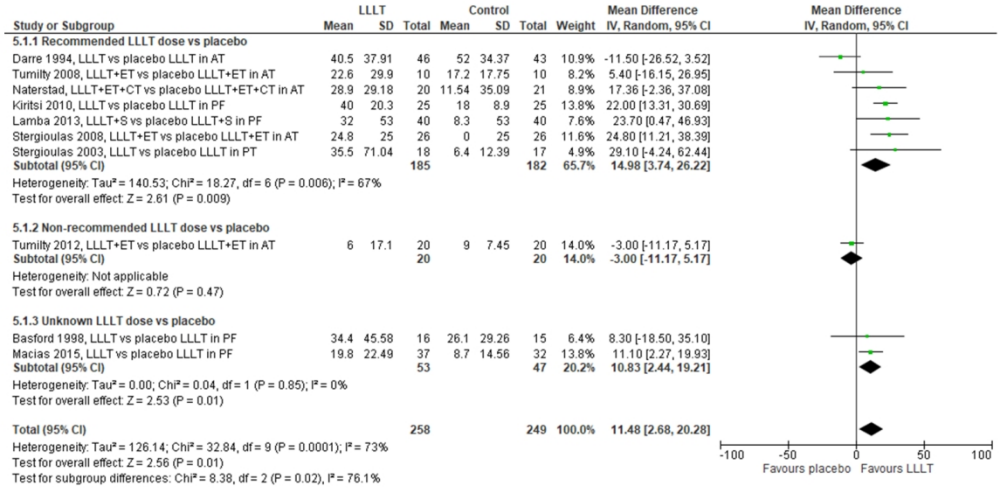

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Supplemental digital content for the article:

Efficacy of low-level laser therapy in patients with lower extremity tendinopathy or plantar fasciitis: systematic review and meta-analysis of randomised controlled trials

Contents

PubMed database search string

("Low-Level Light Therapy"[Mesh] OR LLLT[Title/Abstract] OR “low level”[Title/Abstract] OR “low power”[Title/Abstract] OR laser therap*[Title/Abstract] OR “laser acupuncture”[Title/Abstract] OR “HeNe”[Title/Abstract] OR “632 nm”[Title/Abstract] OR “Ga-Al-As”[Title/Abstract] OR “820 nm”[Title/Abstract] OR “830 nm”[Title/Abstract] OR “850 nm”[Title/Abstract] OR “GaAs”[Title/Abstract] OR “904 nm”[Title/Abstract] OR Photobiomodulation[Title/Abstract] OR phototherap*[Title/Abstract]) and ("Tendinopathy"[Mesh] or tendi*[Title/Abstract] or tendo*[Title/Abstract] or “plantar fasciitis”[Title/Abstract] or "Fasciitis, Plantar"[Mesh] or “Policeman's Heel”[Title/Abstract] or "Iliotibial Band Syndrome"[Mesh] or Iliopsoas tendi*[Title/Abstract] or Jumper*[Title/Abstract] or Patella[Title/Abstract] or Achill*[Title/Abstract] or "Achilles Tendon"[Mesh])

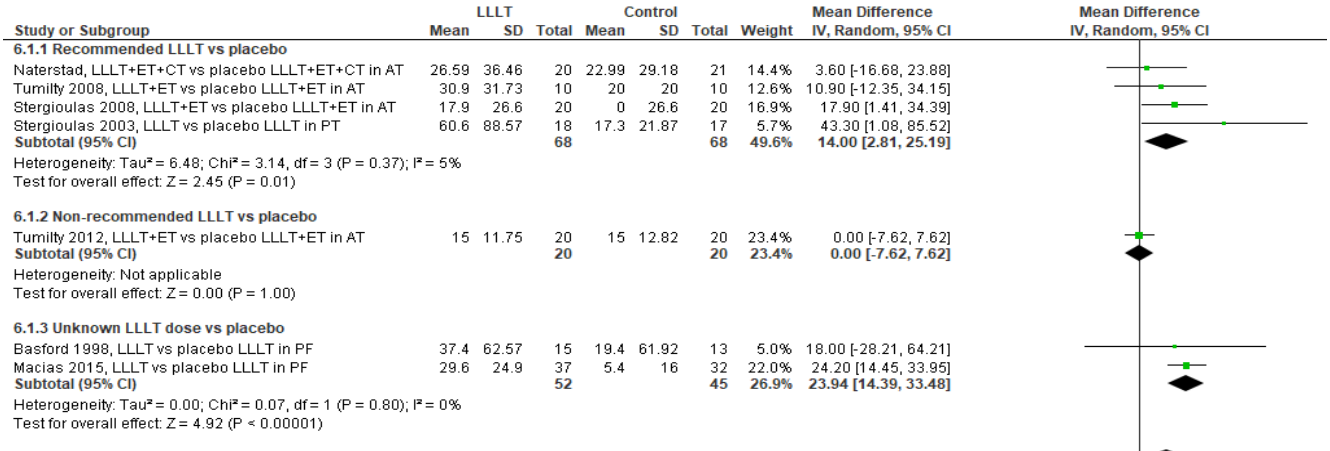
Excluded full text articles

Author/Year/Reference	Reasons for exclusion
Abat et al. 2016[1]	Impossible to isolate effect, combined treatments compared with other treatment
Aigner et al. 1996[2]	No control group
Ashok et al. 2018[3]	Lacks randomisation
Atik et al. 2018[4]	Commentary only
Bjordal et al. 2006[5]	Outcomes of interest not reported
Chang et al. 2015[6]	Outcomes of interest not reported
Cinar et al. 2013[7]	Conference paper only (author contacted)
Cinar et al. 2012[8]	Solely abstract available
Costantino et al. 2005[9]	Not LLLT, high intensity laser therapy
Coughlin et al. 2014[10]	Solely abstract available
Fernandes et al. 1991[11]	Mixed population with unclear inclusion of diagnosis
Foley et al. 2016[12]	Not LLLT, light emitting diode therapy
Jastifer et al. 2014[13]	No control group
Lögdberg-Andersson et al. 1994[14]	Only pooled data on lower and upper extremity available
Mardh et al. 2016[15]	Not LLLT, high intensity laser therapy
Meier et al. 1988[16]	Outcomes of interest not reported
Morimoto et al. 2013[17]	No control group
Mulcahy et al. 1995[18]	Lacks credible control group, includes only 3 patients with tendinopathy
Notarnicola et al. 2014[19]	Not LLLT, high intensity laser therapy
Olivera et al. 2009[20]	Animal study
Orellana-Molina et al. 2010[21]	Outcomes of interest not reported
Saxena et al. 2015[22]	Not LLLT
Scott et al. 2011[23]	Review
Siebert et al. 1987[24]	Mixed population/diagnoses
Simunovic 1996[25]	Narrative review
Suleymanoglu et al. 2014[26]	Conference abstract
Takla et al. 2019[27]	Used a combination of LLLT and light emitting diode therapy
Tumilty et al. 2015[28]	Conference abstract
Tumilty et al. 2016[29]	Not LLLT, high intensity laser therapy

LLLT, low-level laser therapy.

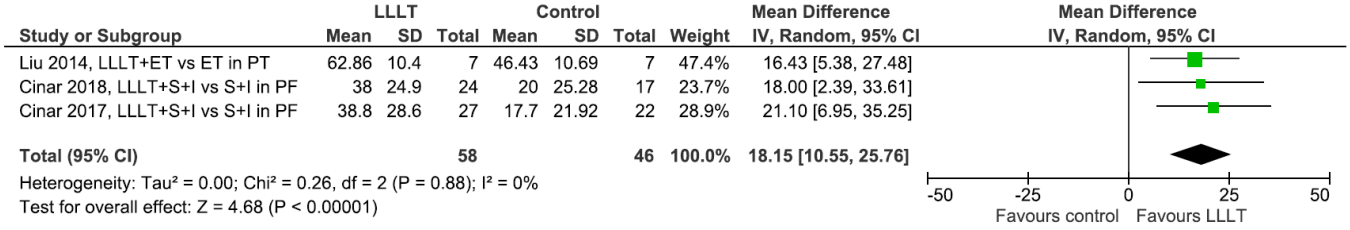
Supplementary figures

Figure S1 Pain at follow-ups 4-8 weeks after completed therapy - LLLT versus placebo



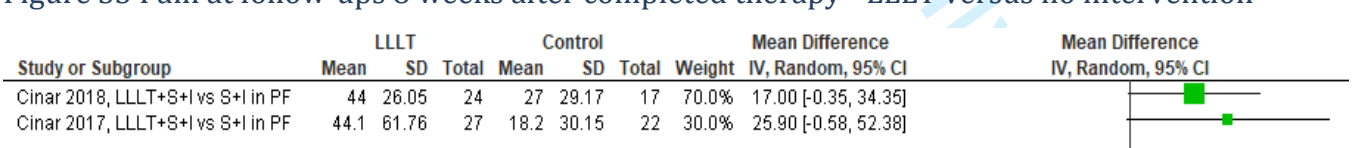
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure S2 Subgroup pain results immediately after completed therapy - LLLT versus no intervention



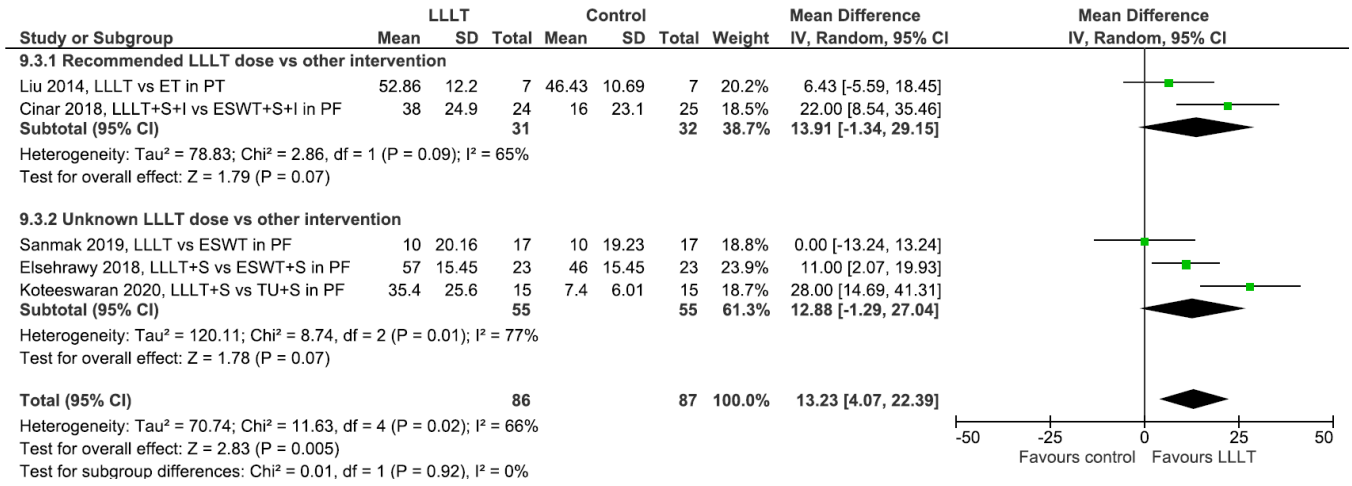
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Figure S3 Pain at follow-ups 8 weeks after completed therapy - LLLT versus no intervention



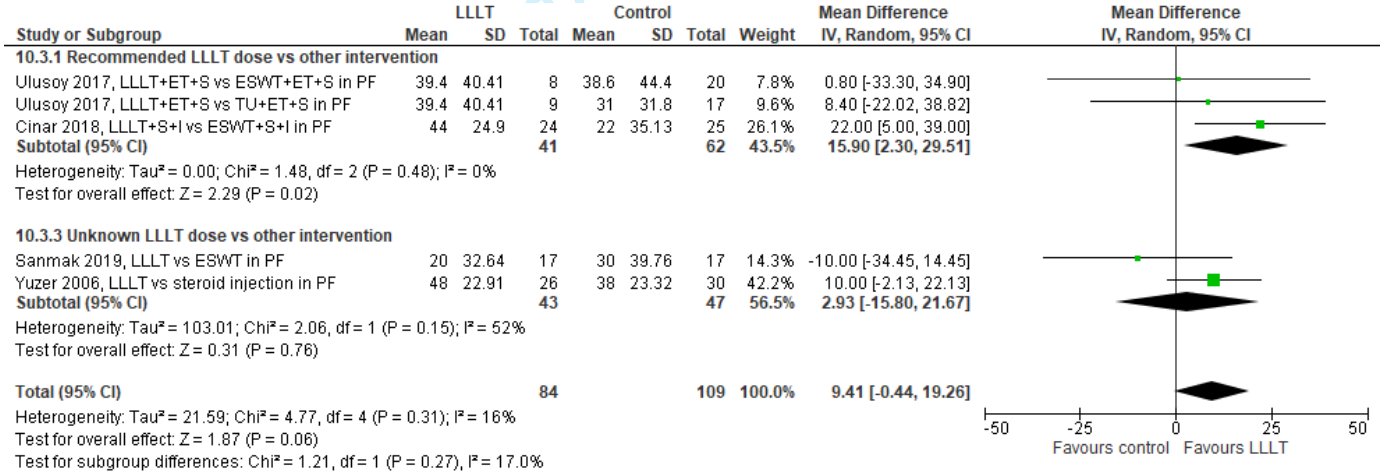
ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; S, stretching.

Figure S4 Overall and subgroup pain results - LLLT versus other interventions



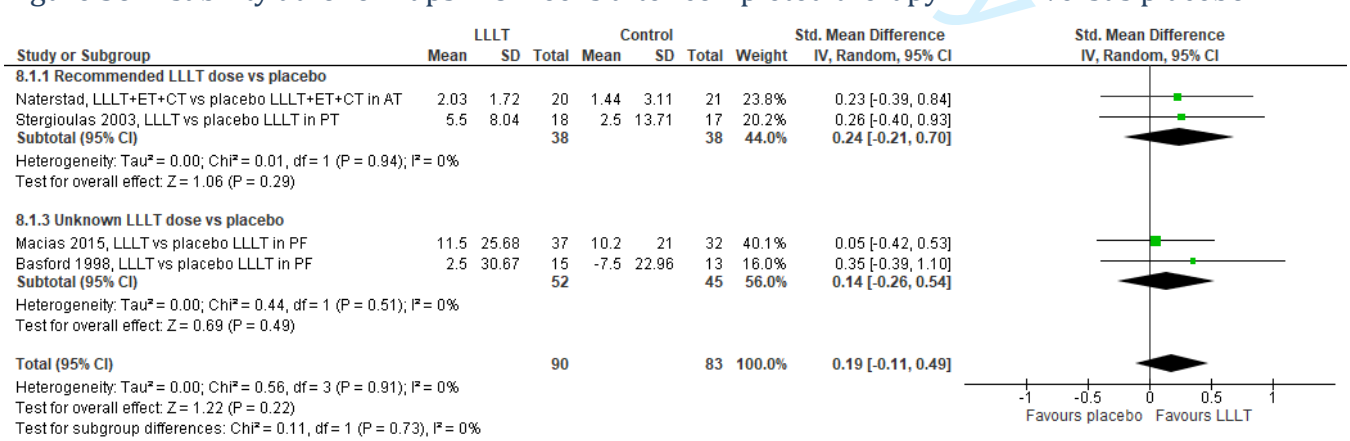
ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S = stretching; TU, Therapeutic Ultrasound.

Figure S5 Pain at follow-ups 4-12 weeks after completed therapy - LLLT versus other interventions



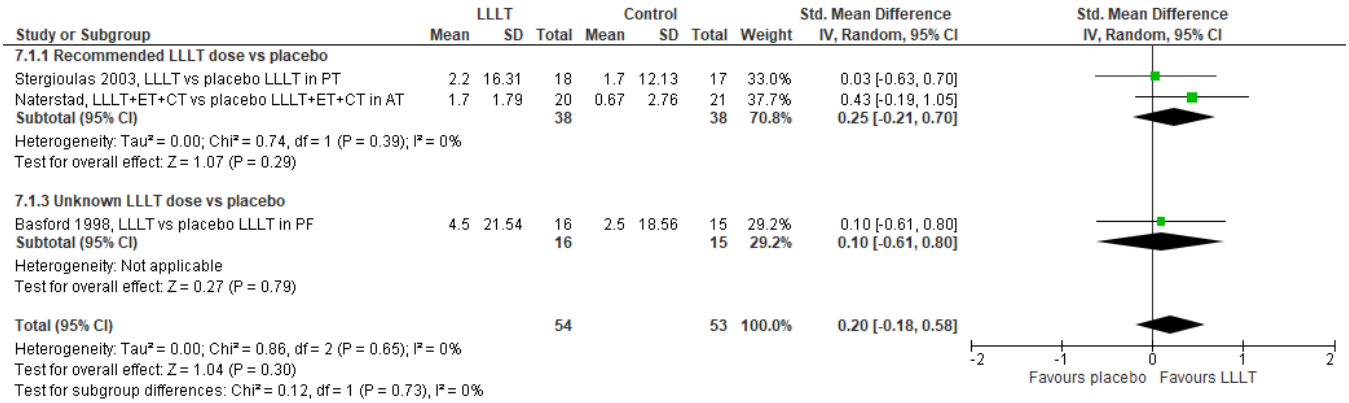
AT, Achilles tendinopathy; CT, cryotherapy; ESWT, Extracorporeal Shock Wave Therapy; ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure S6 Disability at follow-ups 4-8 weeks after completed therapy - LLLT versus placebo



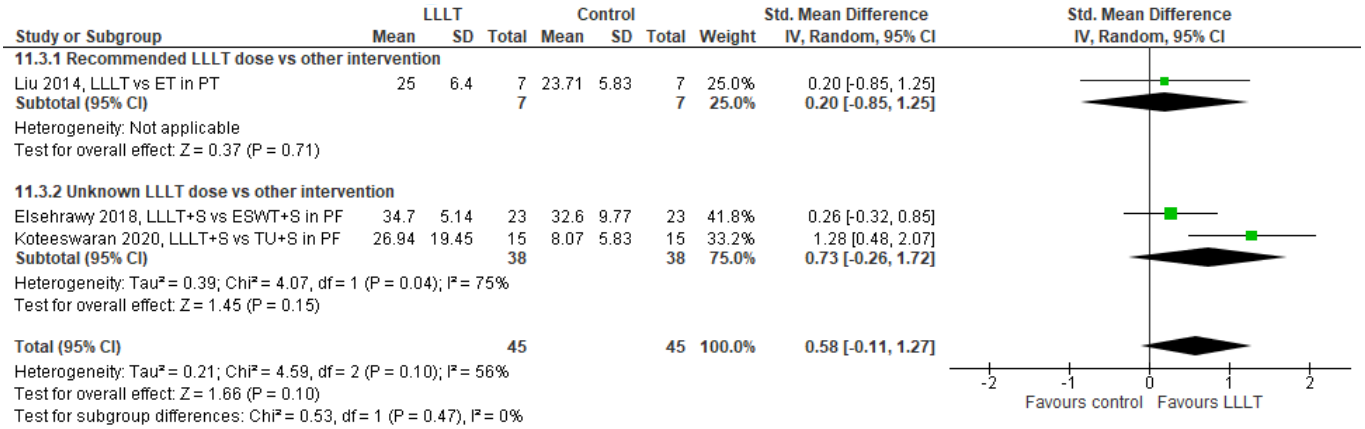
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy.

Figure S7 Disability immediately after completed therapy - LLLT versus placebo



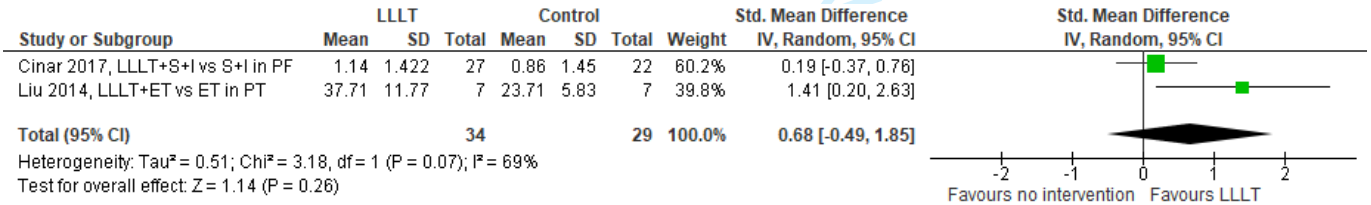
AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy.

Figure S8 Disability immediately after completed therapy - LLLT versus other interventions



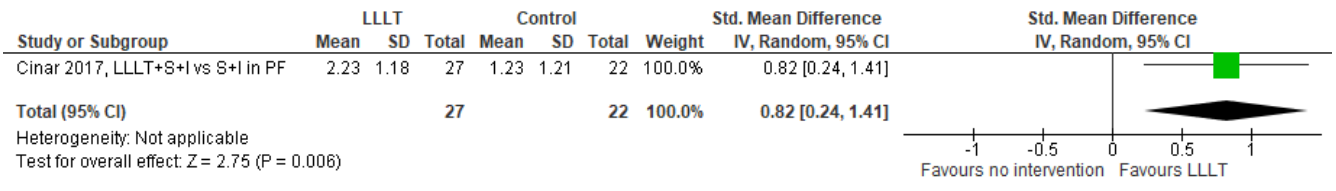
ET, exercise therapy; ESWT, Extracorporeal Shock Wave Therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching; TU, Therapeutic Ultrasound.

Figure S9 Disability immediately after completed therapy - LLLT versus no intervention



ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Figure S10 Disability at follow-up 9 weeks after completed therapy - LLLT versus no intervention

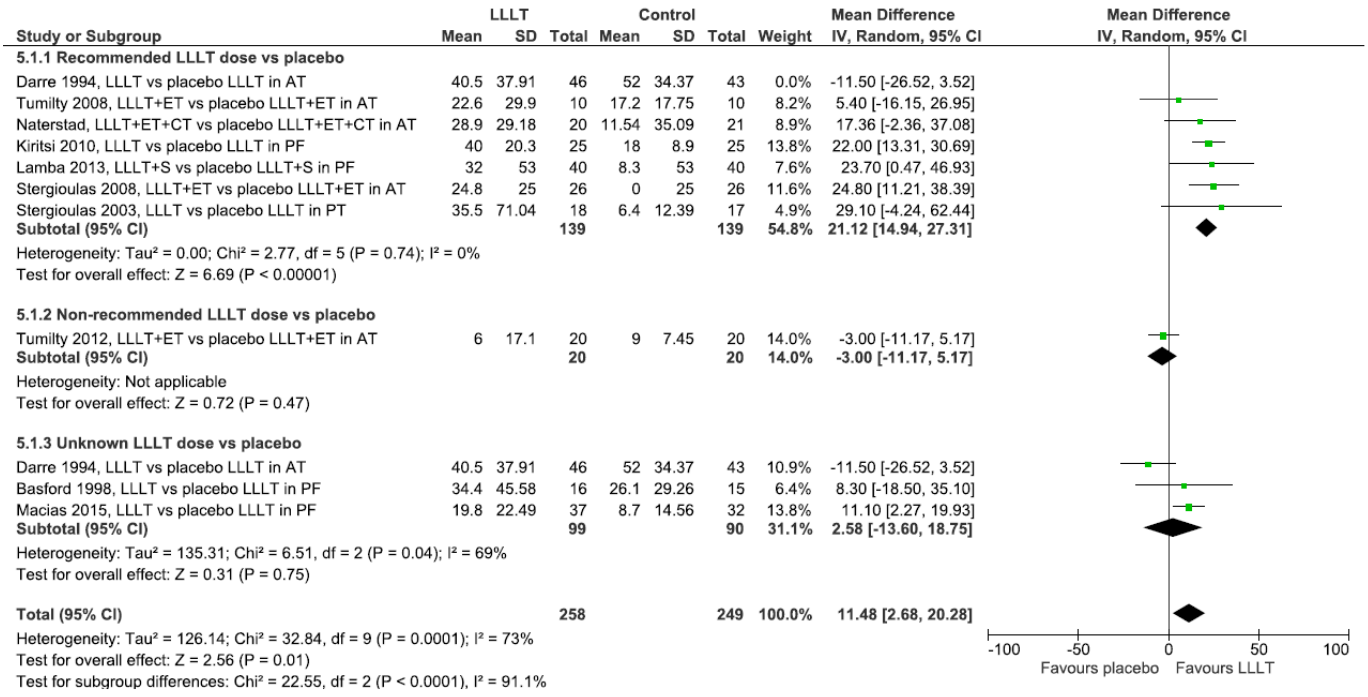


ET, exercise therapy; I, insoles; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Sensitivity analyses

Allocating the study by Darre et al. 1994 to the unknown laser dose subgroup eliminates the statistical heterogeneity in the recommended laser dose subgroup and increases the estimate of placebo-controlled pain reduction to 21.12 mm VAS ((95% CI: 14.94 to 27.31), I^2 = 0%, N = 278) immediately after completed therapy (Figure S11).

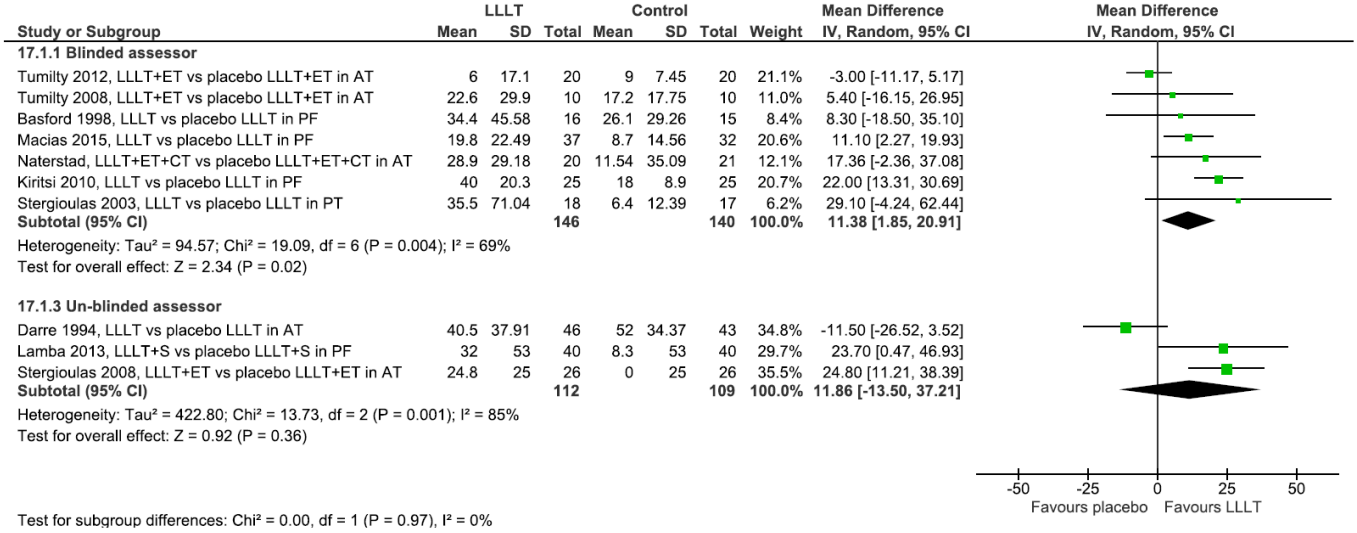
Figure S11 Alternative LLLT dose subgrouping



AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

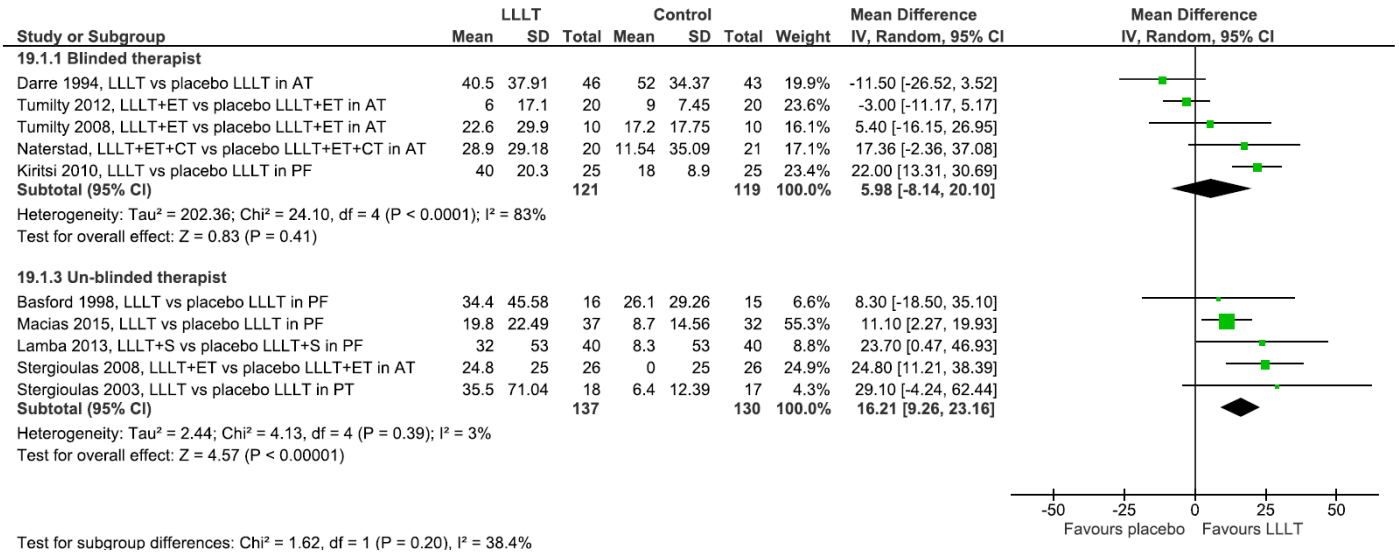
Risk-of-bias within studies post-hoc analyses

Figure S12 Blinded versus unblinded assessor



AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Figure S13 Blinded versus unblinded therapist

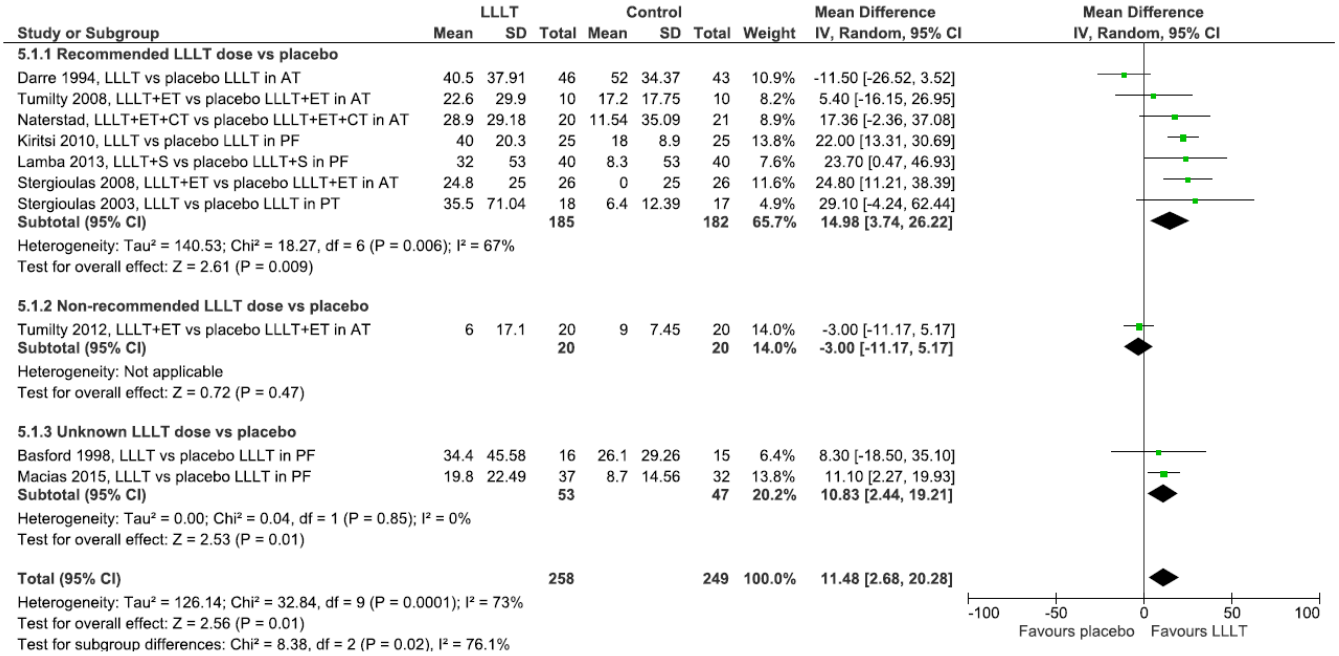


AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Risk-of-bias across studies - random versus fixed effects meta-analysis results of pain

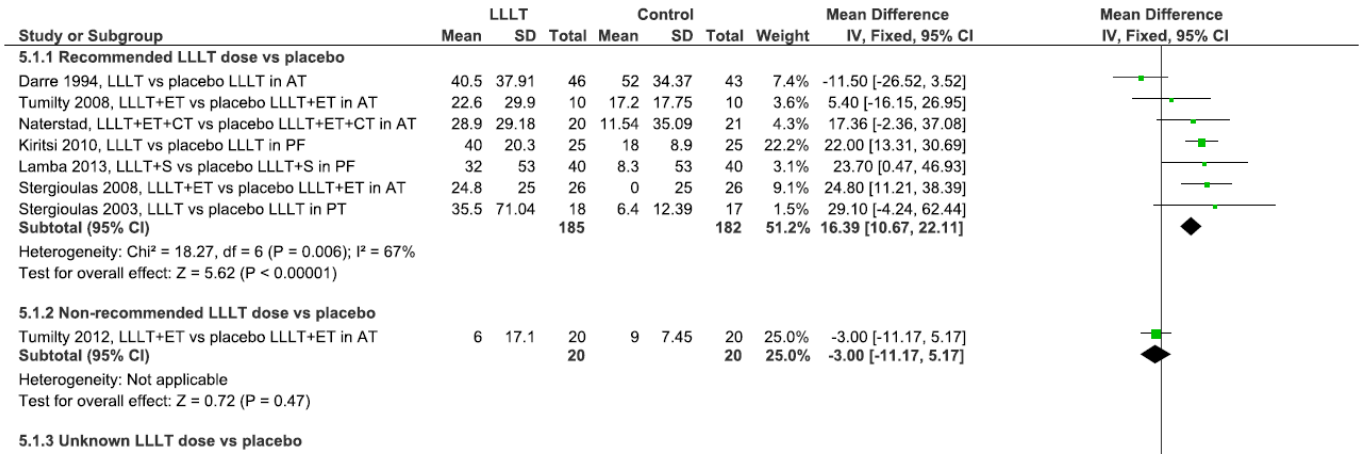
There was almost no difference between the pain point estimates of the random and fixed effects models (pain immediately after the end of therapy), that is, 11.48 mm versus 10.21 mm VAS, indicating that no small study bias exists (Figures S14 and S15).

Figure S14 Random effects meta-analysis model



AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

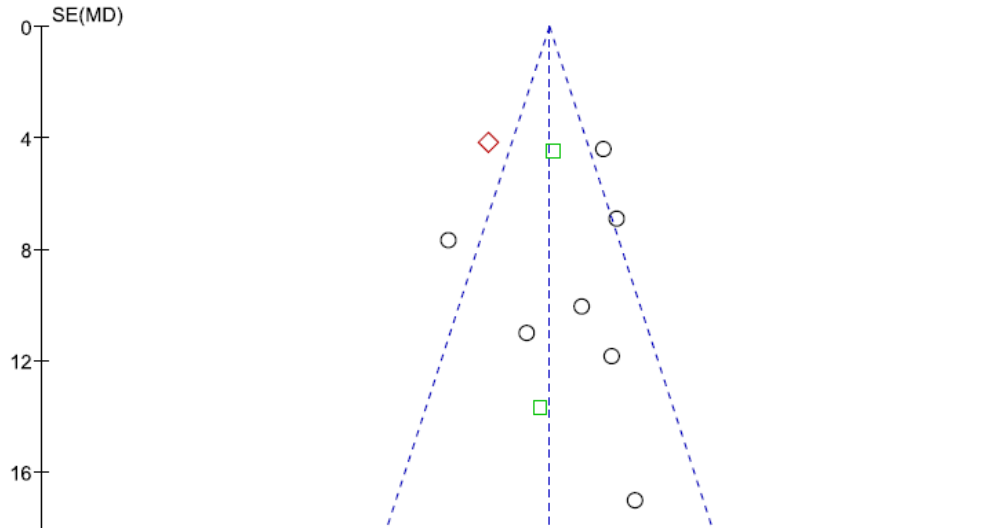
Figure S15 Fixed effects meta-analysis model



AT, Achilles tendinopathy; CT, cryotherapy; ET, exercise therapy; LLLT, Low-Level Laser Therapy; PF, plantar fasciitis; PT, patellar tendinopathy; S, stretching.

Funnel plot of pain results immediately after completed therapy indicating that small study bias is absent (Figure S16).

Figure S16 Funnel plot



LLLT, Low-Level Laser Therapy; MD, mean difference; SE, standard error.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3-4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5, supplemental
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figur 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9, supplemental
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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PRISMA 2009 Checklist