Evidence for Rehabilitation Interventions After Acute Lateral Ankle Sprains in Athletes: A Scoping Review

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Evidence for rehabilitation interventions after acute lateral ankle sprains in athletes: A scoping review

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Rehabilitation after acute lateral ankle sprain

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ABSTRACT

Context: Acute lateral ankle sprain (LAS) is a common injury in athletes and is often associated with decreased athletic performance, and if treated poorly, chronic ankle issues such as instability. The physical performance demands such as cutting, hopping and landing involved with certain sport participation suggests that the rehabilitation needs of an athlete after LAS may differ from the those of the general population.

Objective: To review the literature to determine the most effective rehabilitation interventions reported for athletes returning to sport after acute LAS.

Evidence Acquisition:

Data Sources: Databases Pubmed, Embase, Cinahl, SportDiscus and PEDro were searched to July 2020.

Study Selection: A scoping review protocol was developed and followed in accordance with the PRISMA-ScR guidelines and prospectively registered (https://osf.io/bgek3/). Study selection included published articles on rehabilitation for ankle sprain in an athletic population.

Data Extraction: Parameters included athlete and sport type, age, sex, intervention investigated, outcome measures, measurement tool and follow up period.

Data Synthesis: A qualitative synthesis for all articles was undertaken, and a quantitative sub-analysis of randomized controlled trials (RCT) and critical methodological appraisal was also conducted.

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Evidence Synthesis: 37 articles were included in this review consisting of 5 systematic and 20 narrative reviews, 7 RCTs, a single case series, case report**,** position statement, critically appraised topic, and descriptive study were also included. RCT interventions included early dynamic training, electrotherapy, and hydrotherapy.

Conclusions: Early dynamic training, after acute LAS in athletes, results in a shorter time to return to sport, increased functional performance, and decreased self-reported re-injury. The results of this scoping review support an early functional and dynamic rehabilitation approach when compared to passive interventions for athletes returning to sport after LAS. Despite existing research on rehabilitation of LAS in the general population, a lack of evidence exists related to athletes seeking to return to sport.

Keywords: foot, rehabilitation, physiotherapy, physical therapy, return to sport.

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Introduction

Lateral ligament injuries to the ankle are a common musculoskeletal complaint, with an estimated rate of one ankle injury per 10,000 people per day [1-3]. In a sporting population, the incidence is even greater, constituting 15% to 45% of all sport related injuries [3]. When an athlete sustains a lateral ankle sprain (LAS) this can often result in lost playing time, decreased athletic performance, and if treated poorly, chronic ankle issues such as instability [4]. Additionally, LAS presents a significant economic burden when medical costs and leave from work are taken into consideration [5]. The high frequency of LAS in athletes, alongside the costs of injury management, demonstrate the importance for rehabilitation interventions to be evidence-based.

Research to date, supports non-operative management for excellent long-term outcomes when compared with surgical intervention in cases not involving a complete ligament rupture [6-9]. The increased costs, intra and post-operative complication risks and prolonged absence that are associated with surgical interventions are also reasons that make conservative management more favorable [9-11]. Clinical practice guidelines have been developed with respect to rehabilitation after LAS, however, these do not appear to inform the efficacy of rehabilitation interventions specific to athletes wishing to return to sport (RTS)[10,12].

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Considering the greater physical requirements such as cutting, jumping, hopping and landing associated with certain sport participation it would be reasonable to suggest that an athlete's rehabilitation plan should differ from that of the general population. Therefore, this review aims to scope the literature to determine the most effective rehabilitation interventions reported for athletes returning to sport after sustaining a LAS.

Materials and Methods

Study design

A scoping review study design was utilised to identify key concepts, knowledge gaps and types of evidence currently available and the protocol was prospectively registered with Open Science Framework (https://osf.io/bgek3/)[13].

Data Sources and Searches

Two researchers (ET & JM) conducted the literature search to identify, screen and select studies to be included in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) [14]. The search strategy was developed through the methodological procedure proposed by Arksey and O'Malley [13] and Johanna Briggs Institute [15], and followed a 3-step approach:

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1. A pilot search of the database PubMed using the subject headings: (acute) AND (ankle) AND 'sprain OR injury' AND 'treat* OR manage* OR rehab* OR therap*' AND 'sport* OR athlet* OR 'funct* OR exercis*'.
2. Identified key words and terms relating to acute lateral ankle sprains and rehabilitation interventions and return to sport.
3. Execution of the final search strategy and further searching of referenced lists of the selected articles, including systematic and narrative reviews.

A search was formulated and conducted in five databases (Pubmed, Embase, Cinahl, SportDiscus and PEDro) from inception to 27 July 2020. Articles were downloaded to the EndNote reference management software (http://www.endnote.com/) for selection by ET & JM according to the PRISMA-ScR statement [14].

Study Selection

The eligibility criteria were defined by the *population* (**athletes** clinically diagnosed with acute lateral ankle sprain), *concept* (any study reporting on the effects of rehabilitation interventions for acute lateral ankle sprain) and *context* (all periods of time, outcomes, comparators, follow up, return to sport setting and during and type of intervention). The following types of publications were eligible for inclusion: intervention studies, narrative reviews, scoping reviews, systematic reviews, meta-analysis, case series and clinical commentaries. Exclusion criteria were (1) non-English language, **(2) non athlete only population**, (3) studies involving animals, (4) chronic ankle instability population, (5) fractures and/or dislocations, (6) deltoid ligament,

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peroneal, syndesmosis injuries, (7) preventative interventions, (8) surgical interventions, and (9) pharmacological interventions. The following were also excluded from our review: conference abstracts/proceedings, magazines and newspaper articles, grey literature and in those articles where the full text was not available.

Data Extraction and Quality Assessment

Data extraction, categorization and mapping was performed by ET & JM using methodology adapted from the Joanna Briggs Institute (JBI) guidelines for scoping reviews [15]. The data were extracted into the following categories: (1) author, (2) year, (3) aim/purpose, (4) study population (including demographic details) and size, (5) study design, (6) intervention (type, comparator, duration and details), (7) outcomes, and (8) key findings.

Data synthesis and Methodological quality appraisal

A qualitative synthesis for all articles was undertaken, and a further quantitative synthesis of randomized controlled trials (RCT) and methodological quality appraisal was included. For critical appraisal two reviewers (ET & JM) independently scored studies using the PEDro scale, where disagreement existed a consensus decision was made through discussion. The Kappa coefficient statistic was used to measure the interrater reliability and agreement between the two reviewers [16]. The PEDro scale is a methodological measure of quality used to appraise RCTs, consisting of an 11-item checklist with a maximum possible score of 10 [17]. Studies of good

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quality received a score of greater than 6, fair quality scores were between 4 and 6, and poor studies received scores of less than 4 [18,19].

Results

The search strategy yielded a total 2600 articles, of which 2525 records were removed as duplicates or not meeting the pre-defined inclusion criteria. Upon completion of the title and abstract screening, 75 articles were retrieved and assessed for eligibility. Subsequently, 38 full text articles fulfilled the eligibility criteria and were included (Figure 1).

The number of published studies relating to rehabilitation interventions following LAS to RTS has been consistent over the last 20 years. Of the 37 articles included in this scoping review, 25 were review articles, comprised of 20 narrative reviews and 5 systematic reviews. Also included were a critically appraised topic, position statement and a descriptive study were also identified (Supplementary Figure 1). The five systematic reviews investigated a range of interventions including bracing, functional treatment, cryotherapy, manual mobilisation and exercise [20]. There were also 7 RCTs included, along with a case series, and a case report.

Characteristics of the included reviews

There were five systematic reviews reported in this review containing 82 original studies (Table 1). The methodological quality of the included articles within the systematic reviews were

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classified as poor or limited quality. Additionally, methodological quality was not reported in all of the included reviews[21]. The five systematic reviews contained literature from 1990-2012 and there were several outcomes investigated for the rehabilitation of LAS. Two of the reviews investigated early dynamic training[9,22]. The remaining three articles explored bracing vs functional treatment[21], cryotherapy[23] and exercise and manual therapy[24]. A critically appraised topic was included containing 3 studies exploring deep oscillation therapy in athletes with acute LAS [25]. A position statement from 2012 proposing an evidence-based clinical guideline to treat LAS was also included in this review[10]. This position statement explored the use of early dynamic training, ice and compression, immobilization, electrotherapy and manual mobilizations. Additionally, a descriptive study relating to the clinical application of cryotherapy was also included in this review. The modalities of cryotherapy surveyed included an ice pack, ice pack and cryokinetics, ice immersion, and ice immersion and cryokinetics [26].

Characteristics of the included intervention studies

Participants

There was a total of 830 participants across the 7 RCTs and the overall sex ratio was 57% male and 43% female. All RCTs contained both male and female participants apart from one [27] which included 22 female participants only and the average mean age was 27 years. Two studies involved professional athletes (29%), with the remainder of participants in the five studies (71%) recreationally or competitively active. The type of sport was unspecified in five studies (62.5%). The remainder included the following sports: soccer, football, basketball, mixed martial arts, volleyball, handball and running. Table 2 provides a summary of

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199 participant characteristics across each intervention study including population, type of sport,
200 sample size, age (mean) and gender. The case series contained 3 intercollegiate athletes
201 comprised of 2 males aged 18 and 21 and single female aged 18. The sports of the
202 participants were women's lacrosse and men's basketball and soccer[28]. The case report
203 examined a 29-year-old male Caucasian professional football athlete [29].
204
205 Intervention type and effectiveness
206 The most investigated intervention in the RCTs was early dynamic training (5 studies) [30-34] ,
207 while one study examined the electro modality, non-invasive interactive neurostimulation [35],
208 and one study aquatic therapy [27]. Early dynamic training included a combination of early
209 weightbearing, range of motion (ROM) exercises, proprioceptive or balance training, running
210 and plyometrics, resistance strength training, or functional rehabilitation. Hydrotherapy
211 showed more effective improvements in pain than standard land-based therapy [27]. Non-
212 invasive interactive neurostimulation was effective in improving short-term outcomes, however
213 showed no significant difference in long-term outcomes to RTS [35].
214
215 Early dynamic training was effective in increasing functional performance, strength, postural
216 control, decreasing recess fluid, and a shortened time to RTS [30-34]. All reported key findings and
217 intervention details can be found in Tables 3 and 4, respectively. The case series explored the
218 use of the Mulligan Concept Mobilization with Movement and all three participants from this
219 study showed an increase in pain-free function at the one month follow up [28]. The application
220 of acute hydrotherapy with super saturated hydrogen-rich water for acute LAS was supported

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221 in the case report. This study indicated multi session hydrotherapy within the first 24 hours may
222 provide benefits in terms of pain, swelling reduction, and ROM [29].
223
224 Outcome Measures
225 Although a range of outcome measures were utilized across the included RCTs (Table 4), the
226 most common were those related to pain and swelling. The visual analogue scale (VAS) was
227 frequently used to assess pain while the measurement tool to assess swelling was inconsistent
228 across the studies. Only two RCT's listed time until RTS as an outcome measure [30,34]. The follow
229 up time for an outcome measure varied between studies with the shortest being three days
230 and longest 18 months [34,36]. Not all studies included a follow up assessment [27,30,32]. The case
231 series utilized outcome measures examining pain, functional limitations, balance, and self-
232 reported ability to weight bear [28]. The case report focused on outcome measures relating to
233 pain, swelling and weight bearing during lunge [29].
234
235 Methodological Quality
236 The methodological quality of the seven RCT's was assessed using the PEDro scale
237 (Supplementary Table 1). The methodological quality in the included articles varied, ranging
238 from 3 to 8 points out of a possible 10 (Table 3). The mean PEDro score was 5.42, meaning
239 overall, the studies are classified as fair quality. One study [31] demonstrated poor
240 methodological quality, scoring 3/10. Four studies (57%) were classified as fair quality and two
241 studies (28%) classified as good quality. None of the studies blinded subjects or therapists. All
242 studies had a between group comparison.

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The interrater agreeability between the two reviewers was 81% (6 of 7 items). The Kappa score for the measure of agreement between the two reviewers on the individual validity was 0.86 indicating an almost perfect agreement [16]. The case series noted a limited number of participants, lack of control group, and randomization of selected interventions as a limitation of the study [28]. Similarly, the case report also cited the small number of participants along with a relatively short period of intervention and no medium- or long-term efficacy of topical hydrogen as limitations [29].

Discussion

Main findings

The purpose of this scoping review was to systematically identify the scientific literature reporting on rehabilitation interventions for athletes RTS after acute LAS, and to (1) provide the type and efficacy of interventions utilised (2) summarize the studies completed to date, and (3) identify any knowledge gaps to inform future research. This review demonstrated that while there was supporting evidence for the use of early dynamic training to rehabilitate athletes post-acute LAS, the evidence was of low-moderate quality [30-34]. These findings are consistent with existing literature that recommends a combination of early weight bearing exercises such as proprioception, resistance, plyometric and functional training[37-41].

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An ankle sprain can result in reduced strength and postural control which can increase risk of re-injury and delay RTS. Given the high level manoeuvres associated with sport, rehabilitation interventions targeting strength, force production and functional endurance have shown to have favourable outcomes [30 34 31 32 33]. In the early stages of a rehabilitation program following LAS, hydrotherapy was shown to provide advantages over standard land-based therapy for a sooner RTS [27]. **Following the acute stage, progressive controlled rehabilitation involving jump stretch flex bands and postural sway showed positive outcomes following LAS and should be considered for inclusion to RTS training protocols. Additionally, rehabilitation programs involving plyometric exercises such as cone hops with 180 degree turn and diagonal cone hops improved functional performance after LAS with the combined effect of strength and speed enhancement**[30 31]. While passive treatments such as non-invasive interactive neurostimulation may improve short-term outcomes such as pain, however long-term outcomes show no significant difference on an athlete's ability to RTS [35].

The results of one systematic review favoured of early mobilisation, early exercise and external ankle support, which may allow a safer and quicker RTS [21]. Although this review provided support for functional treatment, the population of interest was not athletes only. Moreover, none of the included systematic reviews had a sole focus on athletes RTS, instead athletes were combined with the general population in all analyses [9,21-23,42]. Most sports require movement patterns that involve a combination of forces in multiple directions, whilst maintaining the need for optimal technique [43]. Given the increased multidirectional forces associated with sports when compared with a typical walking pattern, the increased demands of an athletic population when developing a rehabilitation program should be considered. However, the

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current body of evidence available is largely focused on non-athletic populations or recreational athletes which utilise RTS as a secondary outcome.

Limitations

Limitations of this review include the lack of RCTs available on LAS with respect athletes and RTS and the relatively poor methodological quality of those studies that were available. Although the inclusion criteria for this scoping review was broad, articles not available in English or full text were excluded. Due to the considerable heterogeneity of the interventions and outcomes reported, it remains a challenge for clinicians working with a RTS population to base rehabilitation protocols after LAS on evidence-based practice.

Clinical and Research Implications

Clinicians should utilize the best available evidence within clinical practice to maximize positive outcomes. Through **sport specific** rehabilitation, athletes may report less weakness, and achieve greater return to baseline biomechanics and motor patterns of sporting movements. **Clinicians should monitor the progression through a multidisciplinary approach involving the medical team, coaches and athlete using sport specific outcomes measures, on field performance and the athlete's confidence.** Our findings are consistent with other recommendations which suggest that an active rehabilitation protocol is superior to passive treatment techniques for RTS [12]. A combination of short-term immobilization, external ankle support, and early dynamic training such as proprioception, strength and balance exercises,

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306 should be utilized to produce optimal outcomes for athletes wishing to RTS [9,22,39]. **As previously**
307 **noted, a limitation of this review were the lack of high quality RCTs investigating these**
308 **interventions in an athlete only, RTS population. A consideration for the direction of future**
309 **research would be for clinical trial design on this topic to be of high quality and consistent use**
310 **of relevant outcome measures, such as athlete re-injury utilized.**

311

312 **Conclusion**

313 **The results of this scoping review provide moderate quality evidence to support for an early**
314 **weightbearing and dynamic exercise rehabilitation approach, in contrast to passive or**
315 **restrictive interventions in rehabilitation protocols for athletes after LAS. Given the higher**
316 **physical requirements in certain sports like cutting, jumping and hopping, rehabilitation**
317 **should be specific to these demands.**

318

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322

323

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Tables

Table 1. Summary of included systematic reviews

Author (year)	Title	Aim	Dates	Methodological quality	Number of studies	Key findings
Kemler et al.2011	A Systematic Review on the Treatment of Acute Ankle Sprain Brace versus Other Functional Treatment Types	To evaluate the effectiveness of braces as a treatment compared with functional treatments such as ankle tape and elastic bandages	1990-2009	Not assessed	8	A few individual studies reported positive functional outcomes after treatment with an ankle brace compared with other functional methods
Hubbard et al. 2004	Does Cryotherapy Hasten Return to Participation? A systematic review	To search original research addressing the effect of cryotherapy on return to participation after injury	1967-2003	Poor quality evidence	4	Cryotherapy may have a positive effect on return-to-participation measures with the relatively poor quality of the studies reviewed
Van Der Wees et al. 2006	Effectiveness of exercise therapy and manual mobilisation in acute ankle sprain and functional instability: A systematic review	Critically review the effectiveness of exercise therapy and manual mobilisation in acute ankle sprains and functional instability by conducting a systematic review of RCTs	1966-2005	Poor quality evidence	17	Manual mobilisation has an initial positive effect on dorsiflexion ROM
Petersen et al. 2013	Treatment of acute ankle ligament injuries: A systematic review	To perform a systematic literature review of the last 10 years regarding evidence for the treatment and prevention of LAS	2002-2012	Poor quality evidence	20	Majority of LAS can be managed without surgery. The results support a phase adapted non-surgical treatment of acute LAS with a short-term immobilization for grade III injuries followed by a semi-rigid brace

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Seah et al. 2011	Managing ankle sprains in primary care: what is best practice? A systematic review of the last 10 years of evidence	To summarize the best available evidence in the last decade for managing ankle sprains in the community	2000-2009	Limited	33	Management is not readily agreed. In mild-to-moderate sprains, functional treatment was better than immobilization. In severe sprains, short period of immobilization in a cast/brace results in a quicker recovery than compression bandage alone. Supervised rehabilitation with conventional treatment can be beneficial

Methodological quality was determined by the individual reviewers not the authors of this study. The conclusion stated is that of the included review in reference to interventions for rehabilitation following LAS. The number of original studies is only those included in each review.

Table 2. RCT Study Characteristics

Author (year)	Title	Population	Sport	Number of participants	Age (Mean)	Sex	
						Male	Female
Razzano et al. (2018)	Non-invasive Interactive Neurostimulation Therapy for the Treatment of Low-Grade Lateral Ankle Sprain in the Professional Contact Sport Athlete Improves the Short-Term Recovery and Return to Sport	Professional athletes with a diagnosis of grade I or II LAS that occurred during a contact sport competition	Soccer, football, basketball, mixed martial arts	61	23	27	10
Kim et al. (2010)	Aquatic Versus Land-based Exercises as Early Functional Rehabilitation for Elite Athletes with Acute Lower Extremity Ligament Injury	Professional athletes with isolated grade I or II ligament injury in ankle	Unspecified	22	26	0	22

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Karlsson et al. (1996)	Early functional treatment for acute ligament injuries of the ankle joint	Recreational or competitive athletes with acute (<24 h) grade I or II lateral ligament ruptures	Unspecified	86	22	57	29
Van Der Linde et al. (2011)	Comparative ultrasound study of acute lateral ankle ligament injuries rehabilitated with conventional, and jump stretch flex band programs	Active athletes who sustained grade I or grade II ankle ligamentous injuries	Unspecified	25	21.6	19	6
Holme et al. (1999)	The effect of supervised rehabilitation on strength, postural sway, position sense and re-injury risk after acute ankle ligament sprain	Recreational athletes	Unspecified	92	26	44	27
Ismail et al. (2010)	Plyometric Training Versus Resistive Exercises After Acute Lateral Ankle Sprain	Athletes with grade I or II LAS	Basketball, handball, football, running	22	27	11	11
Hupperts et al. (2007)	Effect of unsupervised home-based proprioceptive training on recurrences of ankle sprain	Recreational athletes with a LAS < 2 months	Unspecified	522	48	136	120

Table 3. Study aims and key findings

Author (year)	Aim	Key Findings/Conclusion	PEDro score /10
Razzano et al. (2018)	To compare the results of improvement of a foot functional score, lower level of reported pain, and return to sports in 2 groups of contact sport athletes affected by a grade I or II LAS	Non-invasive interactive neurostimulation can improve short-term outcomes that can hasten RTS in athletes with acute grade I or II ankle sprain	6
Kim et al. (2010)	To compare outcomes between aquatic and land-based exercises during early-phase recovery from acute lower extremity ligament injuries in elite athletes	Aquatic therapy showed more rapid improvement in pain compared with land-based interventions	6

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Karlsson et al. (1996)	To compare two different non-surgical treatment modalities in patients with grade I and II LAS	Early dynamic training resulted in an earlier RTS	4
Van Der Linde et al. (2011)	To establish the difference in rehabilitation outcomes between the Jump Stretch Flex Band (JSFB) programme and conventional ankle rehabilitation programmes of acute LAS	The JSFB group showed a decrease in anterior/posterior recess fluid, increase in ligament size and shortened time to RTS	5
Holme et al. (1999)	The effect of an early rehabilitation program, including postural training, on ankle joint function after LAS	Supervised early dynamic training showed an increase in isometric ankle strength and postural control	3
Ismail et al. (2010)	To determine the effects of plyometric training versus resistive exercises on muscle strength and function following acute LAS	Plyometric training improved functional performance after LAS with the combined effect of strength and speed enhancement	6
Hupperets et al. (2007)	To evaluate the effectiveness of an unsupervised proprioceptive training programme on recurrences of ankle sprain after usual care in athletes who had sustained an acute sports related LAS	Proprioceptive training program is effective for the prevention of self-reported recurrences	8

Table 4. Intervention and outcome details

Author (year)	Intervention details	Outcome	Measurement tool: Unit	**F**ollow up
Razzano et al. (2018)	Electro-modalities: Non-invasive interactive neurostimulation vs sham device	1. Pain 2. Self-Reported Functional Impairment Walking Ability	1. VAS: 0-10. 2. Inability Walking Scale (IWS): 0-10	2 & 4 months
Kim et al. (2010)	Aquatic therapy: Aquatic Therapy vs Land Based exercise	1. Pain 2. Static/Dynamic Stability (Biodex Balance System) 3. Percentage single-limb support time	1. VAS: 100mm line. 2. Biodex Medical System, Electric scale level 1-3. 3. Instrumented walkway system, GAITRite:	N/A

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		(GAITrite)	seconds	
Karlsson et al. (1996)	Early dynamic training: Compression pads, early weight bearing, ROM training vs compression wrapping, partial weight bearing (PWB) and crutches	1. Stability 2. Pain 3. Swelling 4. Stiffness 5. Work/sport/activities of daily living 6. Running 7. Stair climbing 8. Support	1-8. Orthopaedic surgeon scoring scale: 0-100	18 months
Van Der Linde et al. (2011)	Early dynamic training : Jump stretch flex band program (JSFB) with ultrasound vs conventional ankle rehabilitation with ultrasound	1. Change in ligament size 2. Decrease of fluid in anterior/posterior recess 3. Time until RTS	1-2. Ultrasound machine (7.5 - 14 MHz linear probe): To the closest 0.01mm. 3. Calendar: days	N/A
Holme et al. (1999)	Early dynamic training: Early ankle mobilization, strength, mobility vs supervised physiotherapy	1. Position sense 2. Isometric strength 3. Postural sway	1. Torsiometer: Degrees 2. Dynamometer: Nm 3. Force Platform: Cm	12 months
Ismail et al. (2010)	Early dynamic training: Plyometric training vs Resistive exercises	1. Climbing down-stairs 2. Raising on heel 3. Raising on toes 4. Single limb stance 5. Eversion/inversion strength	1. Stopwatch: seconds 2-3. Number repetitions: Numerical 4. Stopwatch: Seconds 5. Dynamometer: Nm/kg	N/A
Hupperets et al. (2007)	Early dynamic training: Usual care (any form of rehabilitation used by an athlete) vs usual care and proprioceptive training	1. Self- reported Ankle Sprain	1. Number of Incidences: Numerical	12 months

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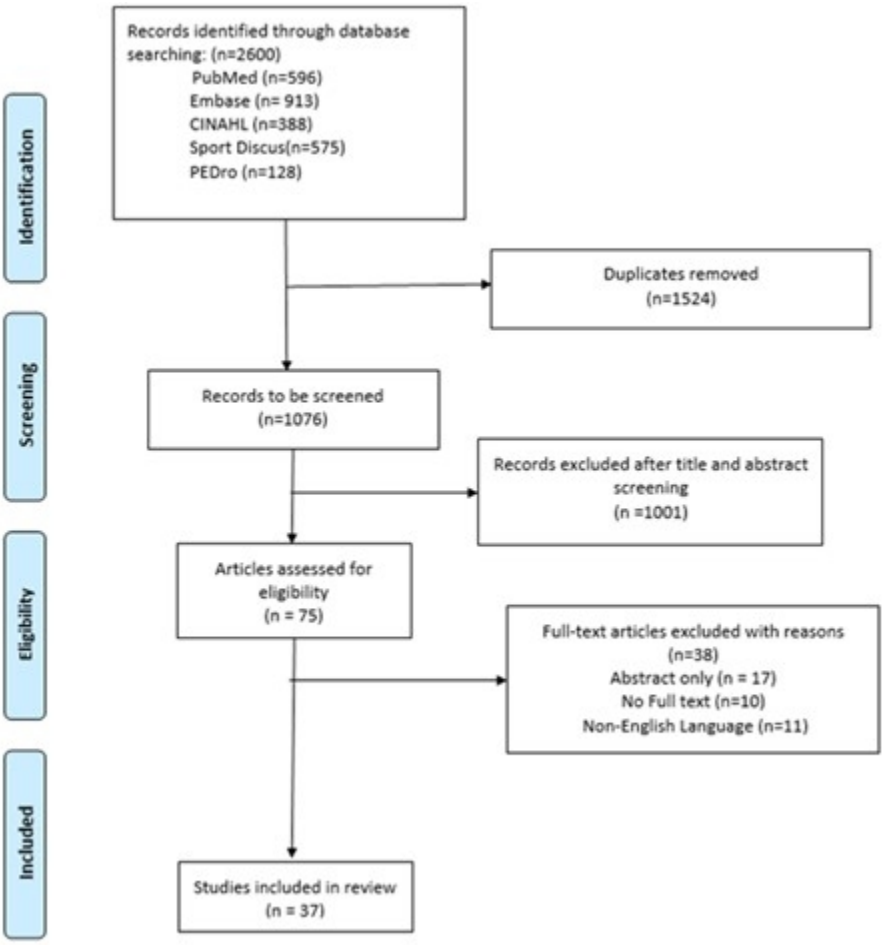

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Supplementary Material

Supplementary Table 1. Results of the methodological quality appraisal (PEDro Scale)

Author (year)	Eligibility	Randomised	Concealed	Baseline	Blinding Subjects	Blinding Therapists	Blind Assessors	Adequate Follow up	Intention-to-Treat Analysis	Between-Group Comparisons	Point estimates and variability	Score
Razzano et al. 2018	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Hupperts et al. 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Eriksson et al. 1996	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	4
Van Der Linde et al. 2011	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	5
Ismail et al. 2010	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6
Holme et al. 1999	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3
Kim et al. 2010	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6

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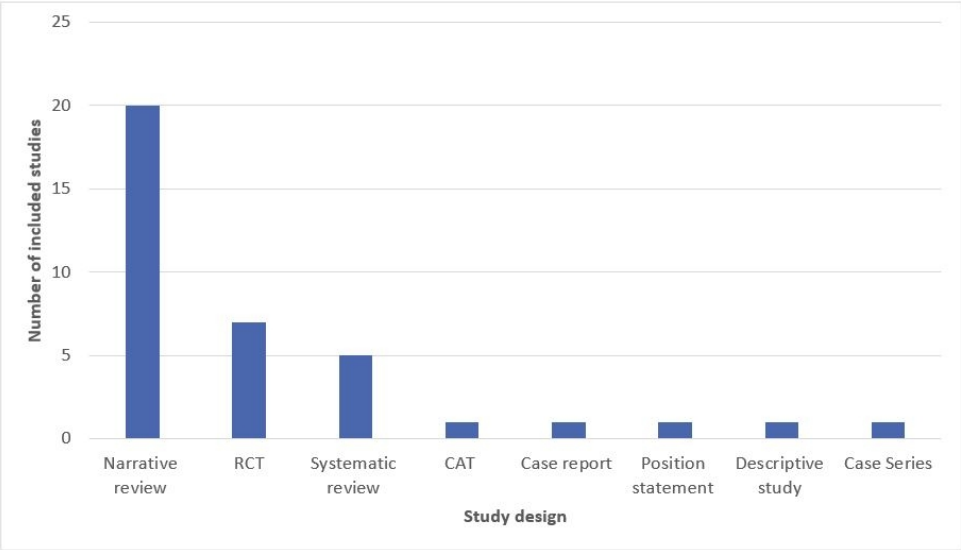
Supplementary Figure 1. Number of included studies by study design type



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