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Systematic review

The role of progressive, therapeutic exercise in the management of upper limb tendinopathies: A systematic review and meta-analysis

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ABSTRACT

Background: Among upper limb tendinopathies, rotator cuff-related shoulder pain and lateral elbow tendinopathy are the most representative disorders. Therapeutic exercise arises as an effective approach, but there is no consensus about the optimal progression criteria.
Objective: To compare progression criteria and effectiveness of isolated, progressive exercises in the management of upper limb tendinopathies. Additionally, to perform a meta-analysis of pain/function for the selected programs.
Design: Systematic Review and Meta-Analysis.
Method: Database search of randomized-controlled-trials including progressive exercise was conducted in PubMed and Scopus until October 2020. Meta-analysis' inclusion criteria were: no data duplicity; 3-months follow-up; comparison between any type of progressive exercise program. Risk of bias was assessed with PEDro score, and level of evidence followed GRADE guidelines. Effect size was calculated with Cohen's d.
Results: Eleven studies were included. GRADE revealed low-quality evidence for meta-analysis of pain during activity (d = 0.29) and function (d = 0.33) at 3 months. Progression criteria were categorised into two divisions, being pain the central concept. Pain (rest/activity/night) and function improved significantly within-group, but between-group changes were heterogeneous. Meta-analysis regarding pain showed good homogeneity with significant, moderate effects (I^2 = 20%; p = 0.005; mean d = 0.29); function yielded important heterogeneity with non-significant, moderate effects (I^2 = 81%; p = 0.17; mean d = 0.33).
Conclusions: Pain was the most frequent benchmark when modulating and progressing the exercises, although other criteria were found such as fatigue or self-perceived ability. Progressive exercise seems effective to manage upper limb tendinopathies, but the superiority of a progression criterion against others remains unclear. Low-quality evidence supported progressive exercise with eccentric components in adding a significant and moderate effect on pain/function at short-term.

1. Introduction

Individuals use upper limbs extremities to perform many activities of daily life and functional movements. Since these tasks usually imply physical strength and repetitive gestures, the risk of dealing with tendon injuries increases (Andres and Murrell, 2008). It is estimated that between 1 and 3% of the general population suffers from upper limb tendinopathies (Scott and Ashe, 2006), with rotator cuff-related shoulder pain (RCRSP) being one of the most common causes of shoulder pain (Lewis, 2009) and lateral elbow tendinopathy (LET) the most prevalent upper limb condition in the working population (Roquelaure et al., 2006).

Therapeutic exercise as a rehabilitation procedure has become increasingly popular during the last 30 years. Researches have shown that tendons undergo adaptations in response to mechanical stimuli, playing progressive loading an important role (Cardoso et al., 2019).

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Moreover, in terms of adverse effects and risks, exercise is expected to cause fewer events in contrast with pharmacological and surgical interventions (Niemeijer et al., 2019), which remain preferable as secondary options.

It is clear that tendons respond to load, and although previous researchers documented similar pathological changes when comparing tendinopathies from different locations, how these adaptations occur in each individual is not yet completely understood (Docking and Cook, 2019). Often, published resistance training programs lack description and calculation of progression criteria, which hinders the standardisation of exercise parameters such as intensity, frequency and repetitions (Cardoso de Souza et al., 2011). That, together with fact that these patients tend to be treated in clinical settings where multimodal approaches are usually necessary and ethical, turns the interpretation of progressive exercise and its absolute benefits into a challenge.

Although lower limb tendinopathies, specifically Achilles and patellar tendinopathy, have drawn abundant studies investigating the effect of therapeutic exercise, upper extremity also demands special attention because of the high incidence of tendon disorders in this region (Werner et al., 2005). Several systematic reviews have been previously completed assessing the effect of exercise for common conditions such as rotator cuff (Kuhn, 2009) and lateral elbow (Cullinane et al., 2014) tendinopathies.

The aims of this systematic review were to compare progression criteria among exercise programs and to assess effectiveness of isolated, progressive exercise programs in the management of upper limb tendinopathies. In addition, we aim to perform a meta-analysis regarding pain and function of the selected exercise programs.

2. Materials and methods

2.1. Design

This systematic review was developed based on the guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2010) and registered in PROSPERO database (Registration: CRD42020173810).

2.2. Data sources and searches

A literature search was performed using PubMed and Scopus from data inception to October 2020, based on Medical Subject Heading (MeSH) and non-MeSH search terms by combining three broad concepts: (i) tendinous tissue, (ii) location of tendinopathy, and (iii) exercise. Extended information about search strategies is provided in Supplemental file A.

2.3. Study selection

Randomized controlled trials (RCTs) meeting the previously established PICO (Population, Intervention, Comparison, Outcomes) were considered the framework of this review. Inclusion criteria were:

(i) Population: patients >18 years, diagnosed with upper limb tendinopathy.
(ii) Intervention: exposure to a progressive exercise programme, which may include, isometric, concentric, eccentric, plyometric, or any other type of exercises without additional equipment such as orthoses, forearm bands, etc. Passive approaches were dismissed to avoid potential underlying effects. Pharmacological and surgical therapies were allowed.
(iii) Comparison: any form of active management, also in isolated manner.
(iv) Outcomes: pain and function.

Exclusion criteria were: (i) non-RCTs or study protocols; (ii) studies in languages other than English or Spanish; (iii) multimodal approaches concurrently with exercise treatment; (iv) exercise program not provided; and (v) subjects with systemic diseases.

Regarding inclusion in meta-analysis, the following criteria was set: (i) no duplicated data from pain or function measurements; (ii) follow-up at 3 months; and (iii) studies comparing any type of progressive exercise program.

2.4. Data extraction

Data was collected according to the following information: participant demographics, duration of the intervention, treatment modalities, characteristics and progression criteria of the exercise programs, outcomes measurements at baseline (T0), end of intervention (T1) and final follow-up (T2), and effect size (Cohen's d). Authors were contacted to ensure that any further details remained out of the analysis.

2.5. Risk of bias

Risk of bias was assessed independently by 2 reviewers with the Physiotherapy Evidence Database (PEDro) score (Maher et al., 2003). Each study was rated from 0 to 10, according to the following items: random allocation; concealed allocation; similarity of groups at baseline; blinding of subjects; blinding of therapists; blinding of assessors; measurements of at least one key outcome; intention-to-treat analyses; reporting of between-group statistical comparisons of at least one key outcome; and providing of variability measures for at least one key outcome. The closer to 10 points, the better the quality of the study.

Risk of bias was independently conducted by two researchers and discrepancies were solved with a third reviewer.

2.6. Data synthesis and analysis

A narrative synthesis from the progression criteria and effectiveness of the exercise programs was conducted, and the extracted data was organised in tables. The intervention showing greater effect sizes was prioritised for between-group comparisons.

Cohen's d from pain and function was calculated to assess the effect size of the different interventions from a "specific-exercise group versus control-exercise group" comparative framework for both pain and functional outcomes, using the formula: $d = (M_2 - M_1)/S_{pooled}$, where d = Cohen's d; M2 = mean from given outcome in experimental group; M1 = mean from given outcome in control group; and Spooled = pooled standard deviation (Cohen et al., 2002). Effect size was classified into 3 categories according to Cohen's suggestions: $d < 0.2$ = small effect size; d between 0.2 and 0.8 = moderate effect size; $d > 0.8$ = large effect size. Adjusted mean of effect sizes for standardized time-points of short-, mid-, and long-term was calculated with the formula: $M = (n_1d_1+n_2d_2+n_3d_3 \ldots)/(n_1+n_2+n_3 \ldots)$, where M = mean; n = sample size; and d = Cohen's d. Cohen's d was presented if the information was available: from baseline to end of the treatment (T0-T1), from baseline to end of the follow-up (T0-T2) and from end of the treatment to end of follow-up (T1-T2). Furthermore, mean effect sizes for the standardized short- (0–4 months), mid- (5–8 months), and long-term (>9 months) time-points were obtained when possible.

Regarding meta-analysis, the Review Manager 5.4 software (The Cochrane Collaboration, United Kingdom, 2020) was used to determine the overall odds ratio. Statistical heterogeneity was assessed with Cochran's Q test and forest plot. Furthermore, I^2 statistic was calculated to quantify heterogeneity, following the next cut-off parameters: not important heterogeneity, 0–40%; moderate heterogeneity, 30–60%; substantial heterogeneity, 50–90%; considerable heterogeneity, 75–100% (Higgins et al., 2019). Results are considered as acceptable if heterogeneity level reaches 0–40%. Significance level was set at 0.05.

2.7. Level of evidence

Level of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which systematically makes judgements about quality of evidence and strength of recommendations (Atkins et al., 2004). According to this framework, systematic reviews of RCTs were primarily classified as designs of high-level evidence grade, which was subsequently downgraded by 1 or 2 levels after considering concerns in the following 5 domains: risk of bias (−1: serious; −2: very serious); inconsistency (−1: important); indirectness (−1: some; −2: major); imprecision (−1: sparse data); and publication bias (−1: high probability). Hence, quality of evidence was categorised as "high" (strong unlikeliness to change confidence in the estimate effect by further research); "moderate" (likeliness to cause important changes in our confidence in the estimate effect by further research, which may change the estimate); "low" (likeliness to cause important changes in our confidence in the estimate effect by further research, which is likely to change the estimate); and "very low" (any estimate of effect is very uncertain).

Level of evidence assessment was independently performed by two researchers. Any discrepancy was solved with a third reviewer.

3. Results

3.1. Study selection

A total of 3570 articles were retrieved from databases, remaining 3416 after removing duplicates. After screening, 51 studies were selected for full-text assessment, finally selecting 11 original articles on qualitative synthesis and 4 articles on the meta-analysis. Further information about selection process is provided in the flowchart from Fig. 1.

3.2. Study characteristics

In total, 11 RCTs were eligible and included in this review. A total of 970 participants were recruited from primary and secondary care hospitals (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Ketola et al., 2017; Østerås et al., 2010; Peterson et al., 2014), waiting lists (Holmgren et al., 2012a; Hallgren et al., 2014) and private outpatient physiotherapy centres (Stasinopoulos and Stasinopoulos, 2017). Subjects with clinical diagnoses of RCRSP (9 trials, n = 816) (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Ketola et al., 2017; Østerås et al., 2010; Hallgren et al., 2014) and LET (2 trials, n = 154) (Peterson et al., 2014; Stasinopoulos and Stasinopoulos, 2017) were analysed, with a mean age of 48.8 years (range 23–65), and 46.7% of female patients. The average number of recruited

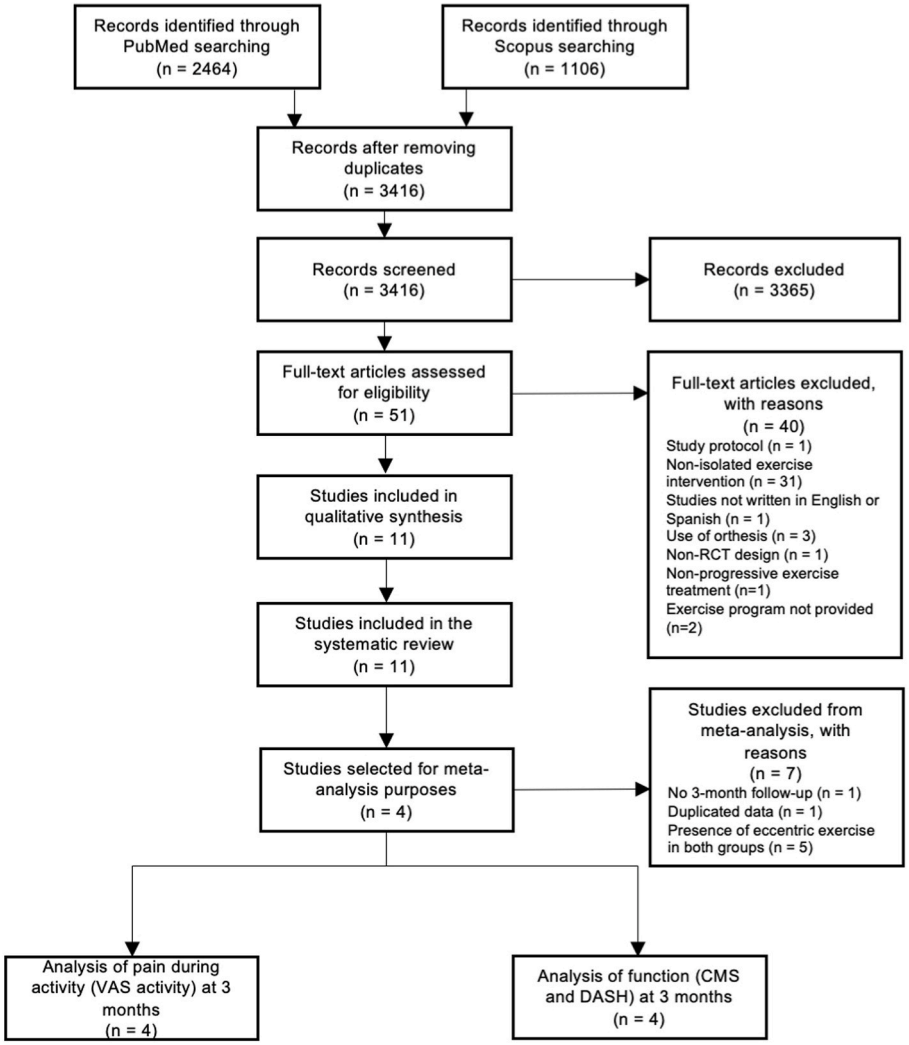

Fig. 1. Flowchart.

patients was 88.2 (range 34–140). Surgery was documented in 3 studies assessing RCRSP: 2 in the experimental group (Brox et al., 1999; Ketola et al., 2017) and 1 in both groups (Hallgren et al., 2014). Further information about baseline characteristics is shown in Table 1.

3.3. Risk of bias

Selected papers ranged from acceptable to good quality, scoring an average of 6.7 (range 5–8). One study showed moderate quality (score = 5) (Ketola et al., 2017) while the other 10 showed high quality (score >6) (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Østerås et al., 2010; Peterson et al., 2014; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017). The items regarding random allocation, baseline comparability, between-group statistical comparisons, and variability/point measurements were accomplished by all the studies; conversely, blinding of subjects and therapists were not fulfilled by any of the studies.

Results from risk of bias analysis are described in Table 2.

3.4. Progression criteria classification

Painful sensation (absence or presence) was founded to be the key benchmark from which the exercises progressed in complexity. Accordingly, progression criteria were categorised into two groups: *Pain Disregard* and *Pain Concern*. Subsequently, they were divided into subgroups according to the role of pain during the progression of the exercises:

1) Pain Disregard

Exercises were performed without taking pain and its related symptoms into consideration (Brox et al., 1999; Peterson et al., 2014).

2) Pain Concern

Painful experience, including its absence or avoidance, was considered while performing the exercises. Based on this subclassification, the following progression criteria were established:

a. Pain Monitoring: pain level as the criterion itself according to predefined stages of the studies, including its alteration, maintenance or absence (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a, 2012b; Østerås et al., 2010; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017).
b. Fatigue-Based: presence of fatigue during the exercise or its overcoming prior to progressing the exercise (Heron et al., 2017).

Table 1
Baseline characteristics.

Author, Year	Design	Sample size (n)	Mean age (years)	Condition	Duration of symptoms (months)	Follow-up (months)	Outcomes	Interventions
Brox et al., 1999 (Brox et al., 1999)	RCT	125	48.0	RCRSP	>3	Baseline/ 3/6/30	Neer score, NPRS, HSC-25	Arthroscopy + exercise (n = 45) vs placebo laser (n = 30) vs supervised exercise (n = 50)
Dejaco et al., 2017 (Dejaco et al., 2017)	RCT	36	50.2	RCRSP	>3	Baseline/ 1.5/3/6.5	CMS, VAS (activity), ROM, isometric abduction strength	Eccentric exercise (n = 20) vs conventional exercise (n = 16)
Ellegaard et al., 2016 (Ellegaard et al., 2016)	RCT	99	48.5	RCRSP	>1	Baseline/ 3/6.5	VAS (rest/activity) SDQ, isometric strength during internal-external rotation and abduction, US	Exercise involved shoulder (n = 49) vs exercise uninvolved shoulder (n = 50)
Hallgren et al., 2014 (Hallgren et al., 2014)	RCT	97	52.0	RCRSP	>6	Baseline/ 3/12	CMS, DASH, VAS (rest/ activity/night), EuroQol (EQ-5D, EQ VAS), US	Specific exercise program (n = 51) vs control exercise (n = 46), both including optional surgery
Heron et al., 2017 (Heron et al., 2017)	RCT	120	49.9	RCRSP	>3	Baseline/ 1.5	SPADI	Open-chain (n = 40), closed-chain (n = 40) and ROM (n = 40) exercises
Holmgren et al., 2012a (Holmgren et al., 2012a)	RCT	102	52.0	RCRSP	>6	Baseline/3	CMS, DASH, VAS (rest/ activity/night), EuroQol (EQ-5D, EQ VAS), US	Specific exercise program (n = 51) vs control exercises (n = 46)
Holmgren et al., 2012b (Holmgren et al., 2012b)	RCT	36	53.2	RCRSP	>6	Baseline/ 1/2/3/6	CMS, DASH, VAS (rest/ activity/night), EuroQol (EQ-5D)	Supervised strengthening (n = 17) vs home exercise (n = 19) programs
Ketola et al., 2017 (Ketola et al., 2017)	RCT	140	47.1	RCRSP	>3	Baseline/ 3/6/12/24	VAS (rest/disability/pain at night/working ability), SDQ	Arthroscopy + exercise (n = 70) vs exercise (n = 70)
Østerås et al., 2010 (Østerås et al., 2010)	RCT	61	43.9	RCRSP	>3	Baseline/ 3/9/15	VAS (rest), SRQ	High-dosage (n = 31) vs low-dosage (n = 30) medical exercise
Peterson et al., 2014 (Peterson et al., 2014)	RCT	120	47.9	LET	>3	Baseline/ 1/2/3/6/ 12	VAS (during MVC/MME), extension strength, DASH, GQL	Eccentric (n = 60) vs concentric (n = 60) exercise
Stasinopoulos et al., 2017 (Stasinopoulos and Stasinopoulos, 2017)	RCT	34	43.7	LET	>1	Baseline/ 1/2	VAS (rest/function), pain-free grip strength	Eccentric (n = 11) vs eccentric-concentric (n = 12) vs eccentric-concentric-isometric exercise (n = 11)

Abbreviations: RCT, Randomized Controlled Trial; RCRPS, rotator cuff-related pain syndrome; LET, Lateral Epicondylar Tendinopathy; NPRS, Numeric Pain Rating Score (0–9); CMS, Constant-Murley Score; HSC-25, Hopkins Symptom Checklist-25; DASH, Disabilities of the Arm, Shoulder and Hand; VAS, Visual Analogue Scale; EQ-5D, European Quality – 5 Dimensions; SPADI, Shoulder Pain And Disability Index; SDQ, Shoulder Disability Questionnaire; SRQ, Shoulder Rating Questionnaire; QGL, Gothenburg Quality of Life; ROM, Range of Motion; US, Ultrasonography; MVC, Maximum voluntary contraction; MME, Maximum muscle elongation; ROM, Range Of Motion.

Table 2
PEDro score and GRADE evaluation.

PEDro score

Author, Year	Random allocation	Concealed allocation	Baseline comparability	Blinding of subjects	Blinding of therapists	Blinding of assessors	Measure of one key outcome from 85% patients	Intention-to-treat analysis	Between-group statistical comparisons	Variability and point measurements	Final score
Brox et al., 1999 (Brox et al., 1999)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Dejaco et al., 2017 (Dejaco et al., 2017)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
Ellegaard et al., 2016 (Ellegaard et al., 2016)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7/10
Hallgren et al., 2014 (Hallgren et al., 2014)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7/10
Heron et al., 2017 (Heron et al., 2017)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7/10
Holmgren et al., 2012a (Holmgren et al., 2012a)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7/10
Holmgren et al., 2012b (Holmgren et al., 2012b)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Ketola et al., 2017 (Ketola et al., 2017)	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Østerås et al., 2010 (Østerås et al., 2010)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
Peterson et al., 2014 (Peterson et al., 2014)	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
Stasinopoulos et al., 2017 (Stasinopoulos and Stasinopoulos, 2017)	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10

GRADE evaluation: Quality of Evidence and Strength of Recommendations

Comparison	No. of participants	Quality Outcome	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Overall GRADE
Progressive ECC alone or in combination vs other than ECC (Dejaco et al., 2017; Holmgren et al., 2012a, 2012b; Peterson et al., 2014; Stasinopoulos and Stasinopoulos, 2017)	294	Pain	Not serious	−1: imprecision	No inconsistency	No indirectness	Unlikely	Moderate
		Function	Not serious	−1: imprecision	−1: inconsistency	No indirectness	Unlikely	Low
Progressive isotonics + ISOM vs Progressive isotonics + ISOM (Ellegaard et al., 2016)	99	Pain	Not serious	−1: imprecision	No inconsistency	No indirectness	Unlikely	Moderate
		Function	Not serious	−1: imprecision	No inconsistency	No indirectness	Unlikely	Moderate
Progressive isotonics vs Non-progressive isotonics, both with optional Sx (Hallgren et al., 2014)	97	Pain	Not serious	−2: imprecision	No inconsistency	No indirectness	Unlikely	Low
		Function	Not serious	−2: imprecision	No inconsistency	No indirectness	Unlikely	Low
OC vs CC vs ROM exercises (Heron et al., 2017)	120	Pain	-	-	-	-	-	-
		Function	Not serious	−1: imprecision	No inconsistency	−1: indirectness	Unlikely	Low
Progressive isotonics + Sx vs Progressive isotonics (Brox et al., 1999; Ketola et al., 2017)	235	Pain	−1: serious	−1: imprecision	No inconsistency	−1: indirectness	Unlikely	Low
		Function	−1: serious	−1: imprecision	No inconsistency	−1: indirectness	Unlikely	Low
HD vs LD exercises (Østerås et al., 2010)	61	Pain	Not serious	−2: imprecision	No inconsistency	No indirectness	Unlikely	Low
		Function	Not serious	−2: imprecision	No inconsistency	No indirectness	Unlikely	Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; ECC, eccentric exercise; ISOM, isometric exercise; Sx, surgery; OC, open-chain; CC, closed-chain; ROM, range of motion; CYC, cycloergometer

Table 3
Exercise programs and progression criteria.

Author, Year	Intervention arms	Reps and frequency	Duration of the program (months)	Treatment characteristics	Progression criteria
Brox et al., 1999 (Brox et al., 1999)	Arthroscopy + specific exercise	NR	6	(Only for the exercise group) Exercises were performed against low resistance. At the beginning, the affected arm performing the exercises was placed in a sling hanging from the roof. Supervision of the exercises occurred twice/week (gradually reduced), and the rest days were performed at home. Three lessons about the anatomy and function of the shoulder, pain management and ergonometrics were also given	NR
	Laser	-	-		-
	Specific exercise	Reps NR, 1 h/day, once/daily	6		Resistance was gradually added over time
Dejaco et al., 2017 (Dejaco et al., 2017)	ECC	3x8-reps exercises, 2 times/daily	3	Exercises were done at home. During the first 6 weeks, patients attended to one physiotherapy session/week, and three sessions/week during the last 6 weeks ECC group performed two eccentric exercises: external rotators using an elastic band, and empty-can abduction in the scapular plane. Pain was accepted if not exceeding 5 on a 0–10 NPRS Control group exercises consisted in eight exercises: full-can abduction in the scapular plane using a dumbbell, external and internal rotation in 0° abduction with an elastic band, shoulder shrugs, prone horizontal abduction and active stretchings for the pectoralis muscles	Load was increased when the exercises could be performed without pain or discomfort, first adding repetitions (to a maximum of 15) and then increasing resistance of the elastic band or dumbbell
	Control exercise	3x8-reps exercises, once/daily			
Ellegaard et al., 2016 (Ellegaard et al., 2016)	Specific exercise in involved arm	10-reps exercises, 3 times/week	2.5	Exercises were done at home. One session/week was supervised by a physiotherapist. Control and strength exercises (eccentric, concentric and isometric) for the scapula were developed during the first 2 weeks, aiming to progress to the strengthening of the rotator cuff muscles. Pain was accepted if not exceeding 5 on a 0–10 VAS. Delayed onset muscle soreness and fatigue were allowed	Load was increased as pain allowed
	Specific exercise in uninvolved arm				
Hallgren et al., 2014 (Hallgren et al., 2014)	Specific exercise	0- to 8-week: 3 × 15 reps, 2 times/daily. 8- to 12-week: 3 × 15 reps, once/daily	3	After 3 months, patients who asked for surgery were operated and, after that, another home exercise program from Holmgren (Holmgren et al., 2012b) was administered	Load was increased if pain experience reverted to before-exercise levels before the next session (Holmgren et al., 2012a)
	Control exercise	10-reps exercises, 2 times/daily (at home) and once every other week at the clinic (Holmgren et al., 2012a)			None (Holmgren et al., 2012a)
Heron et al., 2017 (Heron et al., 2017)	OC exercises	3 × 10 reps, 2 times/day, 3 days over the 6 weeks	1.5	Exercises were done at home. All patients used rubber bands. Pain during exercise was allowed, but not to the extent where its increase affected functionality or worsened for longer than 1 h afterwards. Active stretchings were also taught holding for 5 s, 5 reps, and with the same frequency as the rest of the exercises	Resistance was increased by changing from red to green or black rubber bands, as soon as 10 repetitions could be accomplished without rest. Shoulder abduction also progressed to 90°. Two of the exercises progressed by using only the symptomatic arm, and the third increased in intensity. Progressed from passive-assisted shoulder abduction and rotations to active movements against gravity.
	CC exercises				
	ROM exercises				
Holmgren et al., 2012a (Holmgren et al., 2012a)	Specific exercise	0- to 8-week: 3 × 15 reps, 2 times/daily. 8- to 12-week: 3 × 15 reps, once/daily	3	All patients used weights and rubber bands and simultaneously performed a home exercise program, 1–2 times/daily during these 3 months, monitoring adherence with a diary. The specific exercise group consisted in ECC for the rotator cuff muscles and ECC-CON for scapula stabilisers. Pain exceeding 5 on a 0–10 scale was not allowed, although feeling some pain was recommended. Education on maintaining good posture (straight back, retracted shoulders) was emphasized. Pain after session had to be lower as before,	Load was increased if pain experience reverted to before-exercise levels before the next session
	Control exercise	10-reps exercises, 2 times/daily (at home) and once every other week at the clinic			None

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Intervention arms	Reps and frequency	Duration of the program (months)	Treatment characteristics	Progression criteria
				otherwise load was decreased. The control exercise group performed unspecific movements for neck and shoulder without load.	
Holmgren et al., 2012b (Holmgren et al., 2012b)	Specific exercise Control exercise	First week: 10-reps exercises, 2 times/daily. 2- to 12-week: 2-3x10–15 reps, 2 times/week. 10-reps exercises, 2 times/daily	3	During the first week, both groups performed home exercises to increase ROM, without increasing pain. In addition, patients were educated about daily-life activities that involve lifting the arms above the horizontal, which was contraindicated for the first 4 weeks. In the specific group, supervised exercise progressed from postural correction to ISO, and then to dynamic strengthening with ECC and CON exercises. Leisure and work-related activities were taken into account for the progression. In the control exercise at home, only ROM exercises were maintained.	Increasingly complexity (load, ROM, coordination) was gradually added over time without increasing pain None
Ketola et al., 2017 (Ketola et al., 2017)	Arthroscopy + specific exercise Specific exercise	3 × 30-40 reps, 4 times/week	24	The exercise program was similar in both groups, also made at home simultaneously. Elastic bands and weights were used. Exercises aimed to be performed without pain.	Increasingly complexity (assisted to active, active to strengthening) was gradually added as the self-assessed ability improved
Østerås et al., 2010 (Østerås et al., 2010)	HD exercise LD exercise	3 × 30 reps, 3 times/week 2 × 10 reps, 3 times/week	3	Starting position, ROM and resistance were adapted based on individual sense of comfort, symptoms and clinical findings. Both programs combined global aerobic exercise through CYC (70–80% of maximal heart rate) with local exercises to modulate pain with equipment (pulleys, bench, barbells …). No home exercises were given. The HD group started with CYC 15–20 min; halfway and at the end of the session, subjects cycled for 10 min. The LD group worked with CYC 5–10 min only at the beginning of the session.	Increasingly complexity (load, ROM, starting position) was gradually added over time, always close to pain threshold and under fatigue.
Peterson et al., 2014 (Peterson et al., 2014)	ECC exercises CON exercises	3 × 15 reps, once/daily	3	All patients used a water container with a handle, whose initial load was 1 kg for women and 2 kg for men. The exercise program was performed at home.	Load was increased by 0,1 kg every week
Stasinopoulos et al., 2017 (Stasinopoulos and Stasinopoulos, 2017)	ECC training ECC-CON training ECC-CONC-ISO	3 × 15 reps, 5 times/week	1	All patients used free weights. Interactions between patient and therapist was kept to a minimum. Mild pain (VAS<4) during exercises was allowed until it became disabling (VAS>8)	Load was increased when the exercises could be performed without pain or discomfort

Abbreviations: NR, Not Reported; OC, Open-Chain; CC, Closed-Chain; ROM, Range Of Motion; HD, High-Dosage; LD, Low-Dosage; ECC, Eccentric; CON, Concentric; ISO, Isometric; CYC, ergometer cycle; VAS, Visual Analogue Scale; NPRS, Numeric Pain Rating Scale.

c. Subjective Perception: increase in complexity according to the improvement in patients' self-assessed ability (Ketola et al., 2017).

Table 3 gathers the information about exercise programs and progression criteria.

3.5. Progression criteria results

3.5.1. Pain disregard

Two studies (n = 245) (Brox et al., 1999; Peterson et al., 2014) did not take painful sensation into account for the progression of the exercises. Cohen's d showed small mean values regarding pain and function outcomes at short- (0.17 and 0.08, respectively) (Peterson et al., 2014), mid- (0 and 0, respectively) (Brox et al., 1999), and long-term (0.1 and 0.05, respectively) (Brox et al., 1999; Peterson et al., 2014) stages.

3.5.2. Pain concern

Nine studies (n = 725) (Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Ketola et al., 2017; Østerås et al., 2010; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017) considered painful experience (either its absence or avoidance) when progressing the exercises.

Pain Monitoring criterion was embraced by 7 studies (n = 465) (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a, 2012b; Østerås et al., 2010; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017). Regarding pain, Cohen's d showed small-to-moderate mean effect sizes for pain during rest and activity at short- (0.2 (Ellegaard et al., 2016; Holmgren et al., 2012a; Holmgren et al., 2012b; Østerås et al., 2010; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017) and 0.27 (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a, 2012b; Hallgren et al., 2014), respectively), mid- (−0.3 (Ellegaard et al., 2016; Holmgren et al., 2012b) and 0.1 (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012b), respectively) and long-term (0.44 (Østerås et al., 2010; Hallgren et al., 2014) and −0.23 (Hallgren et al., 2014), respectively) stages; pain at night also yielded moderate mean effect sizes at short- (0.62 (Holmgren et al., 2012a; Holmgren et al., 2012b; Hallgren et al., 2014)) and long-term (0.28 (Hallgren et al., 2014)), with one study showing large

values at mid-term (0.91 (Holmgren et al., 2012b)). Function results showed small-to-moderate mean effect sizes at short- (0.53 (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a; Holmgren et al., 2012b; Østerås et al., 2010; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017)), mid- (0.09 (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012b)) and long-term (0.6) (Østerås et al., 2010; Hallgren et al., 2014) periods.

Fatigue-Based criterion was followed by 1 study (n = 120) (Heron et al., 2017). Only results regarding function at short-term were provided, showing a small Cohen's d mean value (−0.003). Finally, *Subjective Perception* criterion was adopted by 1 study (n = 140) (Ketola et al., 2017). Only long-term results were provided, with small Cohen's d mean values for pain during rest (0.04) and at night (0.08), and for function outcomes (0.08).

3.6. Effectiveness in pain and function outcomes

Pain was assessed in 10 of the 11 studies (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a, 2012b; Ketola et al., 2017; Østerås et al., 2010; Peterson et al., 2014; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017). Outcomes regarding functionality, performance or both were measured in all of them (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Ketola et al., 2017; Østerås et al., 2010; Peterson et al., 2014; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017). Nine studies (7 for RCRSP (Brox et al., 1999; Dejaco et al., 2017; Heron et al., 2017; Holmgren et al., 2012b; Ketola et al., 2017; Østerås et al., 2010; Hallgren et al., 2014) and 2 for LET (Peterson et al., 2014; Stasinopoulos and Stasinopoulos, 2017)) showed significant within-group changes in all treatment arms for pain and function. However, between-group changes varied: 3 studies showed significant changes in favour of specific exercise (Hallgren et al., 2014), high-dosage (Østerås et al., 2010) or eccentric-concentric-isometric contractions (Stasinopoulos and Stasinopoulos, 2017), while 6 studies showed no between-group differences (Brox et al., 1999; Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Ketola et al., 2017; Peterson et al., 2014). The remaining 2 studies found significant between-group changes for function in favour of the specific exercise group (Holmgren et al., 2012a, 2012b); concerning pain, in particular pain at night, it was only significantly greater for the specific exercise group in 1 of them (Holmgren et al., 2012a).

Regarding effect sizes and level of evidence, Cohen's d was obtained from all the included studies, and level of evidence according GRADE framework was reported for all exercise modalities. The studies were divided into 6 subgroups according to exercise characteristics. Detailed information about GRADE assessment for the different subgroups is provided in Table 2.

From a global perspective, Cohen's d showed small-to-moderate mean effect sizes for pain during rest, activity, and night at short- (0.2, 0.24 and 0.62, respectively), mid- (−0.3, 0.06 and 0.2, respectively), and long-term (0.07, −0.06 and 0.11, respectively) periods. Regarding function, Cohen's d showed a moderate mean value at short- (0.37) and long-term (0.21) stages, but small values were found at the mid-term (0.1).

Such mean effect-size estimations tended to increase when: (i) comparing progressive versus non-progressive exercise protocols (Holmgren et al., 2012a, 2012b; Hallgren et al., 2014) at the short- and mid-term for activity- (0.40 and 0.77, respectively) and night-related (0.62 and 0.91, respectively) pain, as well as for function (0.58 and 0.59, respectively); (ii) adding an aerobic component (Østerås et al., 2010) at the short- and long-term for rest-related pain (0.94 and 0.47, respectively) and function (1.3 and 1.59, respectively); and (iii) combining eccentric-concentric-isometric muscle contractions (Stasinopoulos and Stasinopoulos, 2017) at the short-term for rest-related pain (0.4) and function (0.5).

Cohen's d estimations from pain and functional outcomes are shown in Table 4. Details of the descriptive results are shown in Supplemental file B.

3.6.1. Progressive eccentrics alone/in combination versus other than eccentrics

Five studies (n = 294) (Dejaco et al., 2017; Holmgren et al., 2012a, 2012b; Peterson et al., 2014; Stasinopoulos and Stasinopoulos, 2017) compared progressive exercise including an eccentric component alone or in combination against non-eccentric exercise programs. Regarding pain, Cohen's d showed small-to-moderate mean effect sizes for pain during rest, activity, and at night at short-term (0.04 (Holmgren et al., 2012a; Holmgren et al., 2012b; Stasinopoulos and Stasinopoulos, 2017), 0.29 (Dejaco et al., 2017; Holmgren et al., 2012a, 2012b; Peterson et al., 2014) and 0.61 (Holmgren et al., 2012a, 2012b), respectively); at mid-term, two studies showed moderate mean values for pain during rest (−0.45 (Holmgren et al., 2012b)) and activity(0.33 (Dejaco et al., 2017; Holmgren et al., 2012b)), and large values for pain at night (0.91 (Holmgren et al., 2012b)); only 1 study (Peterson et al., 2014) reported long-term evaluations, showing small effect sizes for pain during activity (0.16). Results concerning function showed moderate mean effect sizes at short- (0.35) (Dejaco et al., 2017; Holmgren et al., 2012a, 2012b; Peterson et al., 2014; Stasinopoulos and Stasinopoulos, 2017) and mid-term (0.45) (Dejaco et al., 2017; Holmgren et al., 2012b) for all outcomes; only 1 study (Peterson et al., 2014) reported long-term assessments, showing small effect sizes for DASH and extension grip-strength.

These results were based on low quality of evidence according to GRADE for both pain and function outcomes, downgraded by imprecision (−1 point) and inconsistency (−1 point).

3.6.2. Progressive isotonics with isometrics in both groups

One trial (n = 99) (Ellegaard et al., 2016) compared progressive exercises with eccentric-concentric-isometric parameters in both study groups, comparing its effect on the injured versus the uninjured arm. Results concerning pain reported small effect sizes for pain during rest and activity at the short-term (−0.12 and −0.09, respectively) and for pain during activity at mid-term (−0.07), with a moderate value for pain during rest at mid-term (−0.24). Regarding function, small mean effect sizes were found for all outcomes at short- (0.03) and mid-term (−0.04), with a moderate-size single value at mid-term for external-rotation strength (−0.26).

According to GRADE framework, these results were based on moderate quality of evidence for both pain and function outcomes, downgraded by imprecision (−1 point).

3.6.3. Progressive isotonics versus non-progressive isotonics, both with optional surgery

One study (n = 97) (Hallgren et al., 2014) compared progressive versus non-progressive isotonic exercises, adding the optional choice of receiving surgical treatment. Cohen's d for pain reported moderate values for pain during rest, activity, and at night at short-term (0.23, 0.42 and 0.62, respectively) and for pain during activity and at night at long-term (−0.23 and 0.28, respectively), showing a small effect size for pain during rest at long-term (−0.15). Concerning function, moderate mean values were found at short-term (0.59), but small at long-term (−0.03).

According to GRADE framework, these results were based on low quality of evidence for both pain and function outcomes, downgraded by imprecision (−2 points).

3.6.4. Open-chain versus closed-chain versus range-of-motion exercises

One trial (n = 120) (Heron et al., 2017) included three study groups comparing open-chain, closed-chain and range-of-motion exercises. Only results regarding function were provided, showing a small mean effect size at short-term time-point (−0.003), based on low quality of evidence, downgraded by imprecision (−1 point) and inconsistency (−1

Table 4
Cohen's d, percentage of change and level of significance from pain and function outcomes.

Author, Year (n)	Group comparison (T1/T2 in months)	Outcomes	Cohen's d (time-points in months)			% of change between groups	P between groups	Effect sizes at standardized time-points in months at short- (0–4), mid- (0–8) and long-term (0 - >9)		
			T0 – T1	T0 – T2	T1 – T2			0–4	0–8	0 - >9
PAIN										
Brox et al., 1999 (Brox et al., 1999) (n = 125)	Arthroscopy + SPEC vs SPEC	NPRS activity	NA, but probably close to 0 (T1: 6; T2: 30)			64.29% vs 61.54%	>0.05*	-	NA, but probably close to 0	
		NPRS night				62.50% vs 60%		-		
Dejaco et al., 2017 (Dejaco et al., 2017) (n = 36)	ECC vs Control exercise	VAS activity	0.28 (0–3)	−0.11 (0–6.5)	0.41† (3–6.5)	51.03% vs 52.86%	>0.05*	0.28	−0.11	-
Ellegaard et al., 2016 (Ellegaard et al., 2016) (n = 99)	SPEC involved arm vs SPEC uninvolved arm	VAS rest	−0.12 (0–2.5)	−0.24 (0–6.5)	−0.15 (2–6.5)	44% vs 70.91%	>0.05	−0.12	−0.24	-
		VAS activity	−0.09 (0–2.5)	−0.07 (0–6.5)	−0.02† (2–6.5)	33.68% vs 31.25%		−0.09	−0.07	-
Hallgren et al., 2014 (Hallgren et al., 2014) (n = 97)	SPEC vs Control exercise	VAS rest	0.23 (0–3)	−0.15 (0–12)	−0.39 (3–12)	86.67% vs 80%	<0.05* for VAS night (p > 0.05 for VAS rest and activity)	0.23	-	−0.15
		VAS activity	0.42 (0–3)	−0.23 (0–12)	−0.61 (3–12)	70.49% vs 72.73%		0.42	-	−0.23
		VAS night	0.62 (0–3)	0.28 (0–12)	−0.41 (3–12)	73.91% vs 65%		0.62	-	0.28
Holmgren et al., 2012a (Holmgren et al., 2012a) (n = 102)	SPEC vs Control exercise	VAS rest	0.23 (0–3)	-	-	33.33% vs 0%	>0.05*	0.23	-	-
		VAS activity	0.42 (0–3)	-	-	59.02% vs 37.88%	>0.05*	0.42	-	-
		VAS night	0.62 (0–3)	-	-	67.39% vs 32.50%	<0.05*	0.62	-	-
Holmgren et al., 2012b (Holmgren et al., 2012b) (n = 36)	SPEC vs Control exercise	VAS rest	−0.38 (0–3)	−0.45 (0–6)	−0.19† (3–6)	75% vs 81.38%	>0.05*	−0.38	−0.45	-
		VAS activity	0.37 (0–3)	0.77 (0–6)	−0.46† (3–6)	94.56% vs 64.81%		0.37	0.77	-
		VAS night	0.59 (0–3)	0.91 (0–6)	0.39 (3–6)	94.47% vs 48.65%		0.59	0.91	-
Ketola et al., 2017 (Ketola et al., 2017) (n = 140)	Arthroscopy + SPEC vs SPEC	VAS rest	0.04 (0–24)	-	-	60.94% vs 55.38%	>0.05*	-	-	0.04
		VAS night	0.08 (0–24)	-	-	67.74% vs 60%		-	-	0.08
Østerås et al., 2010 (Østerås et al., 2010) (n = 61)	HD exercise vs LD exercise	VAS rest	0.94 (0–3)	1.38 (0–15)	0.47 (3–15)	79.31% vs 31.15%	<0.05*	0.94	-	1.38
Peterson et al., 2014 (Peterson et al., 2014) (n = 120)	ECC vs CON	VAS mvc	0.16 (0–3)	0.18 (0–12)	0.02 (3–12)	79.54% vs 72.23%	>0.05*	0.16	-	0.18
		VAS mme	0.17 (0–3)	0.13 (0–12)	−0.05 (3–12)	88.42% vs 82.99%		0.17	-	0.13
Stasinopoulos et al., 2017 (Stasinopoulos and Stasinopoulos, 2017) (n = 34)	ECC + CON + ISO vs ECC + CON	VAS rest	0.22 (0–1)	0.25 (0–2)	0.13 (1–2)	76.81% vs 62.86%	<0.05* (p > 0.05 between ECC-CONC and ECC)	0.22/ 0.25	-	-
	ECC + CON + ISO vs ECC		0.30 (0–1)	0.40 (0–2)	0.29 (1–2)	76.81% vs 57.97%		0.3/ 0.4	-	-
	ECC + CON vs ECC		0.07 (0–1)	0.13 (0–2)	0.17 (1–2)	62.86% vs 57.97%		0.07/ 0.13	-	-
FUNCTION										
Brox et al., 1999 (Brox et al., 1999) (n = 125)	Arthroscopy + SPEC vs SPEC	Neer score	NA, but probably close to 0 (T1: 6; T2: 30)			40.91% vs 41.35%	>0.05*	-	NA, but probably close to 0	
Dejaco et al., 2017 (Dejaco et al., 2017) (n = 36)	ECC vs Control exercise	CMS	0.44 (0–3)	0.32 (0–6.5)	−0.12 (3–6.5)	19.86% vs 12.55%	>0.05*	0.44	0.32	-
Ellegaard et al., 2016 (Ellegaard et al., 2016) (n = 99)	SPEC involved arm vs SPEC uninvolved arm	SDQ	0.14 (0–2.5)	0.07 (0–6.5)	0.07‡ (2.5–6.5)	27.31% vs 23.39%	>0.05	0.14	0.07	-
		Abduction strength	0.05 (0–2.5)	−0.05 (0–6.5)	0.10‡ (2.5–6.5)	0.71% vs 2.19%		0.05	−0.05	-
		Internal rotation strength	−0.13 (0–2.5)	0.07 (0–6.5)	−0.20‡ (2.5–6.5)	0.07% vs −1.27%		−0.13	0.07	-
		External rotation strength	0.07 (0–2.5)	−0.26 (0–6.5)	0.31‡ (2.5–6.5)	−1.34% vs 2.53%		0.07	−0.26	-
Hallgren et al., 2014 (Hallgren et al., 2014) (n = 97)	SPEC + Control exercise	DASH	0.47 (0–3)	0.06 (0–12)	−0.53 (3–12)	70% vs 62.86%	<0.05*	0.47	-	0.06
		CMS	0.71 (0–3)	−0.12 (0–12)	−0.62 (3–12)	72.92% vs 76.74%		0.71	-	−0.12
Heron et al., 2017 (Heron et al., 2017) (n = 120)	CC + OC	SPADI	−0.16 (0–1.5)	-	-	16.98% vs 24.49%	>0.05* §	−0.16	-	-

(continued on next page)

Table 4 (*continued*)

Author, Year (n)	Group comparison (T1/T2 in months)	Outcomes	Cohen's d (time-points in months)			% of change between groups	P between groups	Effect sizes at standardized time-points in months at short- (0–4), mid- (0–8) and long-term (0 - >9)		
			T0 – T1	T0 – T2	T1 – T2			0–4	0–8	0 - >9
	CC + ROM		0 (0–1.5)	-	-	16.98% vs 17.65%		0	-	-
	OC + ROM		0.15 (0–1.5)	-	-	24.49% vs 17.65%		0.15	-	-
Holmgren et al., 2012a (Holmgren et al., 2012a) (n = 102)	SPEC vs Control exercise	DASH	0.47 (0–3)	-	-	46.67% vs 17.14%	<0.05* only for experimental group	0.47	-	-
		CMS	0.71 (0–3)	-	-	49.48% vs 20.69%		0.71	-	-
Holmgren et al., 2012b (Holmgren et al., 2012b) (n = 36)	SPEC vs Control exercise	DASH	0.49 (0–3)	0.60 (0–6)	0.11 (3–6)	66.67% vs 34.21%	<0.05*	0.49	0.60	-
		CMS	0.62 (0–3)	0.57 (0–6)	0 (3–6)	55.32% vs 31.11%		0.62	0.57	-
Ketola et al., 2017 (Ketola et al., 2017) (n = 140)	Arthroscopy + SPEC vs SPEC	SDQ	0.05 (0–24)	-	-	68.85% vs 60.17%	>0.05*	-	-	0.05
		VAS disability	0.09 (0–24)	-	-	67.74% vs 59.38%		-	-	0.09
		VAS working ability	0.1 (0–24)	-	-	40.35% vs 33.33%		-	-	0.1
Østerås et al., 2010 (Østerås et al., 2010) (n = 61)	HD exercise vs LD exercise	SRQ	1.30 (0–3)	1.59 (0–15)	0.53 (3–15)	81.01% vs 24.89%	<0.05*	1.30	-	1.59
Peterson et al., 2014 (Peterson et al., 2014) (n = 120)	ECC vs CON	DASH	0.01 (0–3)	0.07 (0–15)	0.07 (3–15)	66.67% vs 65.09%	>0.05*	0.01	-	0.07
		Extension strength	0.12 (0–3)	0.09 (0–12)	−0.03 (3–12)	7.42% vs 3.44%		0.12	-	0.09
Stasinopoulos et al., 2017 (Stasinopoulos and Stasinopoulos, 2017) (n = 34)	ECC + CON + ISO vs ECC + CON	Pain-free grip strength	0.38 (0–1)	0.42 (0–2)	0 (1–2)	191.12% vs 159.62%	<0.05* (p > 0.05 between ECC-CONC and ECC)	0.38/ 0.42	-	-
	ECC + CON + ISO vs ECC		0.52 (0–1)	0.58 (0–2)	0.12 (1–2)	191.12% vs 146.15%		0.52/ 0.58	-	-
	ECC + CON vs ECC		0.12 (0–1)	0.17 (0–2)	0.11 (1–2)	159.62% vs 146.15%		0.12/ 0.17	-	-
	ECC + CON + ISO vs ECC + CON	VAS function	0.22 (0–1)	0.25 (0–2)	0.25 (1–2)	110.26% vs 87.18%		0.22/ 0.25	-	-
	ECC + CON + ISO vs ECC		0.40 (0–1)	0.42 (0–2)	0.12 (1–2)	110.26% vs 79.49%		0.40/ 0.42	-	-
	ECC + CON vs ECC		0.14 (0–1)	0.10 (0–2)	−0.10 (1–2)	87.18% vs 79.49%		0.14/ 0.10	-	-

Abbreviations: n, sample size; T0, baseline; T1, end of treatment; T2, final follow-up; NA, Not Available; NPRS, Numeric Pain Rating Score (0–9); VAS, Visual Analogue Scale; mvc, maximum voluntary contraction; mme, maximum muscle elongation; SPEC, Specific exercise; CC, Closed-Chain exercise; OC, Open-Chain exercise; ROM, Range Of Motion exercise; HD, High-Dosage; LD, Low-Dosage; ECC, Eccentric; CON, Concentric; ISO, Isometric; DASH, Disabilities of the Arm, Shoulder and Hand; CMS, Constant-Murley Score; SPADI, Shoulder Pain And Disability Index; SDQ, Shoulder Disability Questionnaire; SRQ, Shoulder Rating Questionnaire.
Symbols: *, significant changes within-groups; †, values indicating pain increasing in both groups (positive: more in experimental group; negative: more in control group); ‡, values indicating function worsening (positive: more in experimental group; negative: more in control group); §, data extracted from non-parametric assumptions.

point), according to GRADE framework.

3.6.5. *Progressive isotonics plus surgery versus progressive isotonics*

Two studies (n = 235) (Brox et al., 1999; Ketola et al., 2017) compared progressive versus non-progressive exercise, with the experimental group receiving additional arthroscopic treatment. Effect sizes for pain showed small mean values for all pain scales at mid- and long-term stages (<0.08). Small values regarding function were also found for all scales at mid- and long-term (<0.1).

According to GRADE evaluations, these results were based on very low quality of evidence for both pain and function outcomes, downgraded by risk of bias (−1 point), imprecision (−1 point) and indirectness (−1 point).

3.6.6. *High-dosage versus low-dosage exercise*

One study (n = 61) (Østerås et al., 2010) compared high-dosage versus low-dosage protocols in addition to aerobic exercise with cycle-ergometer. Cohen's d regarding pain showed large effect sizes for pain during rest at short- (0.94) and long-term (1.38) stages. In the same vein, results concerning function showed large effect sizes at short- (1.3) and long-term (1.59).

These values were based on low quality of evidence for both pain and function outcomes, downgraded by imprecision. (−2 points), according to GRADE framework.

3.7. *Secondary outcomes*

Some authors reported data from secondary outcomes such as quality of life, which was evaluated in 4 studies (Holmgren et al., 2012a, 2012b; Peterson et al., 2014; Hallgren et al., 2014). One study assessed emotional distress (Brox et al., 1999). Additionally, 3 others (Ellegaard et al., 2016; Holmgren et al., 2012a; Hallgren et al., 2014) performed ultrasonographic examinations to check the status of the affected tissue.

3.8. *Adverse events*

Only 2 studies (Heron et al., 2017; Peterson et al., 2014) recorded the potential adverse events during the development of the exercise programs, but none were reported.

3.9. Summary of the meta-analysis

Significant and moderate effects were found for pain during activity at 3-months follow-up [SMD = −8.4, 95% CI (−14.29, −2.51; mean Cohen's d = 0.29). Heterogeneity regarding pain was tested, with Chi^2 = 3.73, df = 3 (P = 0.29) and I^2 = 20%, which may not represent important heterogeneity.

Concerning functional outcomes, results yielded non-significant and moderate effects for function at 3-months follow-up [SMD = −0.41, 95% (−1, 0.17); mean Cohen's d = 0.33). Heterogeneity values were Chi^2 = 15.83, df = 3 (P = 0.001) and I^2 = 81%, which may represent considerable heterogeneity.

Results from meta-analysis regarding pain during activity (VAS activity) and function (either CMS or DASH) at 3 months are shown in Fig. 2.

4. Discussion

Our review focused on the load progression criteria and the therapeutic effect of isolated, progressive exercise in the management of upper limb tendinopathies. There was a general improvement in almost every group, although followed progression criteria and their effectiveness differed among studies.

4.1. Progression criteria

Painful sensation was commonly considered when progressing the exercises. This could be explained by the crucial role of upper extremities in performing functional daily-life gestures where pain may be present, constant or intermittent, inherently becoming activity dependent.

4.1.1. Pain concern

Overall, progression guidelines tended towards reducing pain and discomfort while performing the exercises. To a lesser extent, the notions of fatigue and self-perception also pivoted around the central criterion of painful sensation.

In those studies where pain was the sole reference to or not to progress (*Pain Monitoring*), the description of "load and complexity gradually added as pain allowed" was the most frequently used criterion. This type of progression goes in line with previous research indeed suggesting that painful exercises might give improved short-term outcomes compared to non-painful ones (Smith et al., 2017). However, some nuances therein were also detected, such as performing the exercise close to pain-free threshold (Østerås et al., 2010), not increasing pain during the exercise (Holmgren et al., 2012b; Hallgren et al., 2014), permitting mild pain (not >5 on a 0–10 scale) (Dejaco et al., 2017; Ellegaard et al., 2016) and reducing it to zero before progressing to the next step (Stasinopoulos and Stasinopoulos, 2017). Interestingly, only 1 study (Holmgren et al., 2012a) actually recommended feeling some pain (not >5 on VAS), but similarly with the rest of the studies and according to the monitoring system (Thomeé, 1997), increased pain had to revert to before-exercise levels prior to the next session. This system helps to establish subjective pain barriers beyond which the intensity should be considered with caution (safe zone: VAS ≤2) or not exceeded (acceptable zone: VAS between 2 and 5), being previously used in the management of other tendon injuries and locations, such as Achilles tendinopathy (Silbernagel et al., 2007), to ensure patient tolerance. Furthermore, previous research suggests painful exercises might give improved short-term outcomes compared to non-painful ones Conversely, Østeras (Østerås et al., 2010) instructed the patients to perform as close to pain-free threshold as possible, based on the findings from Ben-Yishay (Ben-Yishay et al., 1994) supporting that muscles become less competent due to pain and swelling in the tissue. Such observations go in line with those from Brox (Brox et al., 1999), who claimed that muscle performance is pain-dependent. It may be inferred that functional gestures could be improved if subjects achieve a symptom-free state, which could also enhance compliance when confronting an exercise program.

Fatigue-Based sub-criterion referred to the maintenance or increase of effort under which the exercises had to be performed. Progression guidelines relied on the experience of relative discomfort during exercises and its overcoming prior to going further in terms of physical demands and/or exercise complexity. Heron (Heron et al., 2017) included 3 active groups: open-chain, closed-chain and range of motion exercises, which progressed by increasing band resistance, avoiding the use of the asymptomatic limb and changing from passive-assisted to active movements against gravity, respectively. All groups reported significant results, so identifying optimal fatigue levels remains elusive. It is known that tendons display unique molecular, structural, and mechanical adaptations to fatigue loading (Fung et al., 2010). Therefore, establishing a standard fatigue-loading approach allowing for accurate control over the applied parameters would offer valuable possibilities when progressing and thus modulating tendon responses.

Finally, *Subjective Perception* concerns a particular increase in the complexity according to subject's self-perceived ability to perform the

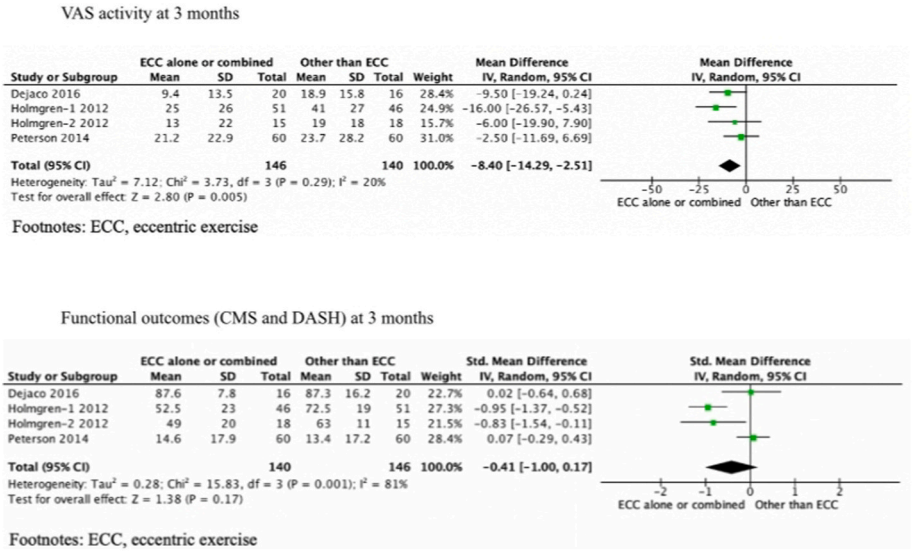

Fig. 2. Meta-analysis forest plots_pain&function.

exercises with proper strength and reliability. Ketola (Ketola et al., 2017) evaluated progression during the control visits, which were also extended until both patient and therapist interpreted that the established exercise complexity could be independently maintained. This prolonged therapist-patient interaction might have led the patients to a greater sense of security and self-confidence, thus affecting motivational and adherence-to-treatment components.

4.1.2. Pain disregard

Only 2 studies (Brox et al., 1999; Peterson et al., 2014) progressed the exercises without taking pain into consideration. Both of them loaded gradually over time, but, in contrast with Brox (Brox et al., 1999), Peterson (Peterson et al., 2014) set a regular increase of 0.1 kg every week. This systematic method of loading may lack exercise individualisation, as individual capability may vary from one subject to another. This could also apply to the determination of the ideal starting weight, which was set as a standard for every patient to simplify its clinical application. In this sense, tailoring the initial load may lead to more precise results and optimum effects, also helping to monitor individual pain tolerance and to guide the progression of the exercises over time as patient's ability improves.

4.2. Pain and function

4.2.1. Rotator cuff-related shoulder pain

Eccentric exercise has been widely used for RCRSP and in other locations, such as in the Achilles tendon (Magnussen et al., 2009). Five of the 9 included studies (Dejaco et al., 2017; Ellegaard et al., 2016; Holmgren et al., 2012a, 2012b; Hallgren et al., 2014) examined eccentric contractions with conflicting results reported. There seemed to be a slight trend of larger effect sizes when adding eccentric contractions to the exercises and comparing progressive versus non-progressive protocols (Holmgren et al., 2012a, 2012b; Hallgren et al., 2014), although 2 studies setting progression criteria in both groups (Dejaco et al., 2017; Ellegaard et al., 2016) did not exhibit such differences. These findings match with those from recent literature, suggesting that eccentric exercise may provide a clinical but uncertain improvement in pain and function compared with other types of exercise (Ortega-Castillo and Medina-Porqueres, 2016; Larsson et al., 2019). In fact, the most promising results and highest Cohen's d estimations (at T1, 0.94 and 1.30 for pain and function, respectively) were provided by 1 study (Østerås et al., 2010) incorporating aerobic exercise, especially in the group performing at a higher dosage. It is hypothesised that gate control mechanisms are strongly activated when exercising at higher intensities, inducing the release of endogenous neuropeptides with strong analgesic effects (Boecker et al., 2008), which could also add value to the physiological bounties of these approaches in combination.

Unlike other common tendinopathies (i.e., patellar, Achilles), RCRSP involves the diagnosis and management of multi-joint demands. While Achilles programs can focus on single-joint exercises like calf raises as the primary treatment strategy, this could differ for the shoulder region based on electromyographic analyses from Reinold and Wilk (Reinold et al., 2004), who found that a wide variety of muscle-activity patterns and strength developments could be evoked from different exercises, depending on which tissue was primarily stimulated and how that influenced the rest of the joint. Such natural complexity of the shoulder could thereby explain why the true effect of the existing exercise principles still remain unclear and challenging to comprehend.

4.2.2. Lateral elbow tendinopathy

The management of LET is also typically characterised by the use of eccentric activation. Two of the included studies assessed this condition, with 1 of them showing that a combination of eccentric-concentric-isometric exercise had greater benefits than eccentric alone or combined with concentric contraction (Stasinopoulos and Stasinopoulos, 2017). Cohen's d calculations for this combined modality were also higher than those estimated from Peterson's study (Peterson et al., 2014), where only eccentric and concentric exercises were compared. This is consistent with the findings from Martinez-Silvestrini (Martinez-Silvestrini et al., 2005), who stated that, unlike in other locations, LET is usually related to activities involving grip efforts and requiring isometric forces. Park (Park et al., 2010) also found significant improvements when performing isometrics, however not implementing any progression. Such information added to the fact that many LET studies incorporate other concomitant conservative modalities hinders the evaluation of the true effect of the exercise progression itself. However, the positive results of the trial which included isometric and eccentric exercise (Stasinopoulos and Stasinopoulos, 2017) suggest this strategy could be clinically useful.

4.2.3. Homogeneity of the studies

Our meta-analysis showed differences in homogeneity when comparing the assessments from pain and function. The forest plot regarding function showed an important heterogeneity between the studies, with both studies from Holmgren (Holmgren et al., 2012a, 2012b) as the only ones indicating that progressive eccentric exercises caused significant improvements in functional outcomes. However, a potential bias could be drawn in this manner, as the rest of the studies placed themselves over the null-effect line, showing the overall meta-analysis not only irrelevant and inconsistent effects, but also imprecise results. Larsson et al. (2019) also performed a meta-analysis to evaluate the post-treatment effects of eccentric exercise for pain and function in the management of RCRSP, and their findings regarding function agreed with ours, since any substantial differences when comparing exercise programs were present.

Interestingly, our meta-analysis regarding pain at 3 months, in fact, indicated a difference in favour of considering eccentric exercise as part of the program, with a moderate mean effect size (0.29) being slightly greater than that from the rest of the studies at such time-point. However, only 1 of them (Holmgren et al., 2012a) showed a significant effect against the control group. Previous research has shown that the benefits from exercise are especially relevant in the early phases of rehabilitation (Thorstensson et al., 2006), which may explain our meta-analysis' findings for pain. It is also important to mention that 9 of the studies included in our review set the duration of the programs at no longer than 3 months (Dejaco et al., 2017; Ellegaard et al., 2016; Heron et al., 2017; Holmgren et al., 2012a, 2012b; Østerås et al., 2010; Peterson et al., 2014; Hallgren et al., 2014; Stasinopoulos and Stasinopoulos, 2017), indeed with significant within-group changes in almost all of them. Due to the heterogeneity among exercise regimens, we decided to prioritise the presence of eccentrics, alone or in combination, as the core element to be meta-analysed against other muscle contractions, but considering the results forthcoming from our analysis, generalizations regarding the effectiveness and appropriateness of a certain exercise modality remains questionable.

4.3. Strengths and limitations

This review has some strengths to be mentioned. To our knowledge, it constitutes the first attempt to address the role of isolated, progressive exercise in upper limb tendinopathies, also providing effect size estimations. We proposed a new approach to various criteria from which exercises may progress based on the patients' report of pain. Since pain usually entails the main reason for consultation among patients, we provided a general scheme with multiple progression criteria from which painful symptoms while exercising could be modulated.

However, some limitations should be recognised. First, we set restrictive inclusion criteria to isolate the therapeutic effect of progressive exercise, hence leaving potential studies with interesting progression guidelines out of the analysis. Second, although all authors were contacted, effect sizes from some original sources could not be obtained, thus basing the calculations on the available data. Third, details

regarding the specific muscle contraction when performing the exercises were missed from many of the studies, which prevents general assumptions between different exercise programs from being made. In the same vein, data concerning patients' opinions about the exercise programs was not provided by any of the studies, which could be an interesting area for further research in order to help clinicians prescribe exercise in a more suitable manner.

5. Conclusions

The analysis of the included studies revealed a predominance of *Pain Monitoring* category as the main benchmark from which the exercises may progress in difficulty, although other pain-modulating variables were found such as fatigue or self-perceived ability.

Progressive exercise, especially with eccentric and aerobic components, seems to be an effective approach in reducing pain and improving function in patients with upper limb tendinopathies, but the superiority of a certain progression criterion against others remains unclear.

This review found low-quality evidence that progressive exercise with eccentric components added a significant and moderate effect on pain and function at the short-term. The contradictory results of existing studies and the lack of homogeneity among exercise programs demands particular focus not only on approaching a potential exercise program acting as a gold standard, but also on investigating new progression criteria that may be supported by the current literature for the management of upper limb tendinopathies.

Ethical approval

Not required.

Patient consent for publication and participation

Not required.

Availability of data and material

All data relevant to the study are included in the article or uploaded as supplementary information.

Authors' contributions

MO-C revised the design, conducted the systematic search, conducted study selection, quality appraisal, acquired data from selected studies, developed statistical analysis and interpretation, and wrote the manuscript.

MT-F reviewed study selection, quality appraisal, helped interpreting acquired data and co-wrote the manuscript.

AL-T supervised statistical analysis and interpretation and made substantial contributions.

AC-V is guarantor, designed the study, validated study selection, quality appraisal, acquired data from selected studies, reviewed statistical analysis and interpretation, and drafted the manuscript.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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