Title: Effectiveness of the Eccentric Exercise Therapy in Physically Active Adults with Symptomatic Shoulder Impingement or Lateral Epicondylar Tendinopathy. A Systematic Review

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TITLE:

Effectiveness of the Eccentric Exercise Therapy in Physically Active Adults with Symptomatic Shoulder Impingement or Lateral Epicondylar Tendinopathy. A Systematic Review.

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TITLE: Effectiveness of the Eccentric Exercise Therapy in Physically Active Adults with Symptomatic Shoulder Impingement or Lateral Epicondylar Tendinopathy. A Systematic Review.

a. Abstract

Objective: To identify and criticise the evidence for the effectiveness of the eccentric exercise to treat upper limb tendinopathies.

Design: Systematic review.

Methods: Relevant randomized controlled trials (RCTs) were sourced using MEDLINE, SPORT Discus, Physiotherapy Evidence Database (PEDro), and CINAHL databases. Inclusion criteria were: (1) studies in English or Spanish; (2) adult participants with clinical diagnosis of tendinopathy; (3) RCT study design; (4) results regarding pain or strength were assessed; and (5) eccentric exercise was employed to treat upper extremity tendinopathies. Two blinded reviewers independently extracted data concerning trial methods, quality and outcomes. PEDro scale was employed to assess methodological quality. Results were summarized in a best evidence synthesis.

Results: The selected studies (n=12) scored an average of 6/10 based on the PEDro score. In 11 studies, pain decreased significantly with eccentric exercise, but only in 5 studies, the reduction was significantly better than in the non-eccentric group (in all or some of the parameters). Strength was assessed in 9 studies; within-group evaluations show that strength significantly improved in the eccentric-group in 7 studies, whereas inter-group changes were only significantly better in the eccentric-group in 3 studies for all the parameters and in 2 studies for some of the parameters.

Conclusions: Eccentric exercise may reduce pain and improve strength in upper limb tendinopathies, but whether its effectiveness is much better than other forms of treatment remains questionable. Further investigations are needed, not only focused on

shoulder impingement or epicondylar tendinopathy, but on tendinopathies in other areas of the upper limb.

b. Key Words

Tendon, overuse injury, eccentric exercise, systematic review.

c. Main body of the text

i. Introduction

Sport medicine is becoming relevant, being tissue degeneration a common finding in many sport-related tendon complaints[1]. In the last twenty years, sports activities have become increasingly important in our modern society[2]. More than 30% of sport injuries arise from or have an element of tendinopathy[3]. Tendinous injuries and other tendon diseases represent a therapeutic and diagnostic challenge[1].

As part of common upper limb tendinopathies, the incidence of Lateral epicondylitis (tennis elbow) in tennis players of all ages is as high as 9 to 4

0%[5,6], and between 1-3% in the general population, being 2 to 3.5 times more frequent in people over the age of 40, particularly if playing tennis more than 2 hours per day[6]. It is estimated that shoulder tendinopathies prevalence within physical workers is 15-20%, and hand and wrist tendinopathies between the interval ranging from 4 to 56%. The risk increases when high strength, repetitions or exposure to vibrations during repetitive work are combined[7]. On the other hand, De Quervain´s disease, caused by stenosing tenosynovitis of the first dorsal compartment of the wrist (abductor pollicis longus and extensor pollicis brevis), is probably the best known form of tendinopathy of the wrist and hand and is approximately six times more common in women than in men[5]. This condition is the third most reported tendinopathy of the upper extremity in physical workers and it is promoted by diabetes or rheumatoid arthritis[7].

Some controversy exists and there is little evidence supporting the use of conservative treatments such as ultrasound (US), iontophoresis with NSAIDs, deep transverse friction massage (DTFM), or acupuncture for treating tendinopathy[8–10]. Nevertheless, in some studies these treatments show positive effects in the reduction of pain or in improvement in the function of patients with tendinopathies (e.g. lateral epicondylitis)[10–13]. Other therapies, including extracorporeal shock wave therapy (ESWT)[14,15], glyceril trinitrate patch[16], percutaneous tenotomy[17], and injection of substances such as autologous blood[18], corticosteroid[19], prolotherapy[20], or platelet-rich plasma (PRP)[21], may be considered if patients do not respond to the mentioned treatments and remain limited significantly in function or activity due to pain[22].

The failed healing response which apparently underlies tendinopathy has been proposed to be counteracted by eccentric exercise (EE) through promoting collagen fibre cross-linkage formation within the tendon, thereby facilitating tendon remodeling[2]. The lack of knowledge regarding pathophysiology of tendinopathy and the ultimate mechanisms by which EE may help resolve tendinopathy remain nowadays hard to determine. Beyond this, it is crutial that the clinical effectiveness of physical modalities such as EE is established as a matter of priority.

Although most eccentric exercise research regarding tendinopathies has classically focused on the lower extremity (specifically Achilles and patellar tendinitis), the upper extremity also warrants scrutiny because of the high incidence of tendon problems[6]. Exercise programmes incorporating eccentric muscle activity are becoming increasingly popular as they are considered to provide a more effective treatment than other forms of exercise therapy[23]. However, in everyday life, only around 60% of patients take advantage of this exercise regime[24].

The objectives of this systematic review are the following: (1) to identify studies investigating the effect of eccentric exercise on upper extremity tendinopathies; (2) to describe the supplemental forms of treatment used in combination with eccentric exercise

protocols in the treatment of tendinopathies; (3) to evaluate the strength of evidence supporting the use of eccentric exercise to treat tendinopathies; and (4) to make recommendations for future research.

ii. Methods

The study protocol was developed based on the framework outlined in the guidelines provided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement)[25]. The registration of this systematic review was properly accomplished in PROSPERO. The registration identifier of the protocol is CRD42014009952[26].

A literature search was performed using MEDLINE, SPORT Discus, CINAHL and Physiotherapy Evidence Database (PEDro) to gather information relating to the treatment of upper extremity tendinopathies with eccentric exercise. Each database was searched since its start date. Study details extracted were organized in two tables: synopsis of the selected studies (pathology, duration of symptoms, intervention, outcome, post-treatment follow-up and PEDro score) were summarized in Table 1, and parameters of the eccentric strengthening protocols (description, frequency/week, duration, sets, reps, progression of the intensity) can be found in Table 2. Two authors (MO and IM) independently searched the databases. This systematic review followed PRISMA recommendations.

The search terms for this systematic review were obtained based on MeSH (*Thesaurus*) and they were: *tendon, tendinopathy, exercise, eccentric, training*.

The articles finally included in this systematic revision were filtered depending on the following criteria: (1) studies in English or Spanish; (2) adult participants with clinical diagnosis of tendinopathy; (3) studies design was RCT; (4) results regarding pain or strength were assessed; and (5) eccentric exercise was employed to treat upper extremity tendinopathies. The studies were obtained from each database, in order of relevance, using these inclusion criteria and only reading title and abstract. Those which could be clearly determined that did not meet the criteria were excluded. Two authors (MO and IM)

independently screened titles and abstracts, and if necessary full texts, to determine whether the paper met the inclusion criteria. The papers of which the authors' opinion was initially different were discussed until consensus was reached.

The methodological quality of each of the studies was assessed independently by two reviewers (MO, IM) using the PEDro criteria. Reviewers were not masked to trial identifiers such as authors' and journals' names. The scored portion of the PEDro scale assesses 8 items pertaining to internal validity and 2 items added to ensure that the statistical results would be interpretable to the reader. Regarding score, 1 point was given if the item was accomplished and 0 points if not, reaching a maximum of 10 points. The closer the score was to 10, the better the quality of the study[27,28].

Results were analyzed using a rating system with levels of evidence for each extracted outcome[29].These levels are:

• Strong evidence: consistent findings among multiple high quality RCTs;

• Moderate evidence: consistent findings among multiple low quality RCTs and/or one high quality RCT;

• Limited evidence: one low quality RCT; Conflicting evidence: inconsistent findings among multiple trials;

• No evidence from trials.

For the purpose of this review, consistency was defined as similar results between trials for a particular outcome. In this review, since blinding the patient and/or treating therapist would have been unlikely, the cutoff for a high quality trial was 5/10 or better; 4/10 was established as moderate quality and 3/10 or below as low quality.

For each continuous outcome between-group effect sizes were reported with 95% confidence intervals. Categorical variables were reported as ratios (percentages) when possible.

Two authors (MO and IM) independently extracted data from the selected studies regarding: (i) authors; (ii) sample size; (iii) location of tendinopathy; (iv) treatment group; (v)

control group; (vi) outcome measure; (vii) previous treatments; (viii) PEDro score; and (ix) the variables in the eccentric exercise protocol, such as description of the exercise, sets, repetitions, time of rest, progression of the intensity, and frequency per week. Other information obtained included group sizes and sociodemographic data (age, gender), length of symptoms, dominance according to tendinopathy, previous treatments, and follow-up post-treatment. Any discrepancies will be resolved through discussion until consensus is reached.

iii. Results

The number of full-text studies retrieved and the number of studies excluded are reported in Figure 1.Reasons for exclusion included: tendinopathies were not treated (n=1); participants were cadavers (n=1); participants were non-human (n=1); eccentric work was not mentioned for the treatment of tendinopathies (n=1); RCT design was not respected (n=2).

The mean PEDro score for the 12 studies was 6/10, with a range from 3 to 8. Overall, these scores are relatively good, considering that the intervention of eccentric exercise does not allow for blinding of the participant or therapist. Blinding of the assessors and concealed allocation were two other criteria that was poorly reported in most of the selected studies. Thus, the highest achievable score was 8/10. The two reviewers had initial agreement on 112 out of 120 criteria (κ = 0,861), and reached consensus on all criteria.

The 12 selected studies included a total of 668 participants with clinical diagnoses of epicondylar tendinopathy (n=355)[30–37] or shoulder impingement (n=191)[38–41]. The average number of participants in each trial was 55.6 (range from 20 to 120; eccentric group mean=25.9; control group mean=28.1) and the mean duration of symptoms at baseline ranged from 1 to 156 months.

Table 1 gathers the results of the 12 studies included in this systematic revision. Pain was assessed in all of them using the VAS (*Visual Analogue Scale*), except in one study, in which SPADI (*Shoulder Pain And Disability Index*) scale was employed. In 11 studies[30–40],

pain decreased significantly in the group where eccentric work was employed as therapeutic modality ($p<0.05$) (in one of them[32], the result is regarding pain in 4 out of the 5 VAS, except during rest); in the remaining study[41], no significant improvement within-group was found in the eccentric-group ($p=0.71$), showing the non-eccentric group (manual mobilizations, stretching, motor control training) a higher and moderate improvement ($p=0.26$), but reflecting both groups non-significant changes. Regarding inter-group changes, in 2 studies[37,41] were significantly better for the non-eccentric group (Cyriax massage-Mill's manipulation and manual mobilizations-stretching-motor control training respectively) ($p<0.05$ and $p=0.046$ respectively), except at 0 weeks evaluation (right after the first session)[37], when no significant different were found; in 7 studies[31,32,34–36,39,40], significant differences were not registered between groups (in one of them[40], the result is regarding pain during rest and activity; in another[36], the result corresponds to all of the evaluations, except at week 8); in 5 studies[30,33,36,38,40], changes were significantly better in the eccentric-group (in one of them[40], the result is regarding pain during night; in another[36], the result corresponds to the evaluation at week 8). Moreover, 2 studies used other tools for pain assessment (apart from VAS): PRFEQ (*Patient Rated Forearm Evaluation Questionnaire*)[35] and VNRS (*Verbal Numeric Rate Scale*)[41]. In the first one[35], significant within-group improvements were found in the eccentric-group, although they were not significant between groups. In the second study[41], within-group changes were moderately better for the non-eccentric group (manual mobilizations, stretching, motor control training), not being significant in the eccentric-group; regarding inter-group changes, they were significantly better in the non-eccentric group in 1 out of the 3 evaluated tests (significant in Neer test, not in Hawkins and empty can tests).

Functional status was assessed in 9 studies, with the DASH (*Disabilities of the Arm, Shoulder and Hand*) questionnaire[30,31,35,38,40], TEFS (*Tennis Elbow Function Scale*)[33,37], SPADI[39] or SDQ (*Shoulder Disability Questionnaire*)[41]. Regarding the DASH questionnaire, 4 studies[30,35,38,40] showed significant within-group changes in the eccentric-group ($p<0.05$), and one study[31] reflected little changes, not being significant; in terms of inter-group changes, 2

studies[31,35] did not show significant differences, and 3 studies[30,38,40] reflected changes significantly better in the eccentric-group ($p<0.05$). Concerning the TEFS, 2 studies[33,37] showed significant within-group changes in the eccentric-group ($p<0.05$); in terms of inter-group changes, one study[37] showed moderately better improvements in the non-eccentric group (Cyriax massage and Mill's manipulation) ($p=0.74$), and another study[33] resulted in significantly better changes in the eccentric-group ($p<0.05$). With regards to the SPADI, one study[39] showed significant within-group improvements in the eccentric-group ($p<0.001$), although between group differences were not significant. Regarding the SDQ, 1 study[41] reflected non-significant within-group changes in the eccentric-group, but they were significant in the non-eccentric group (manual mobilizations, stretching and motor control training) ($p=0.006$); in terms of inter-group changes, they were significantly better in the non-eccentric group ($p=0.025$). To sum up, and with regards to within-group changes, 7 studies[30,33,35,37–40] improved the functionality of the participants in the eccentric-group, and 2 studies[31,41] had non-significant changes in that group; in terms of inter-group changes, in 2 studies were moderately[37] and significantly[41] better in the non-eccentric group (Cyriax massage-Mill's manipulation and manual mobilizations-stretching-motor control training respectively), in 3 studies[31,35,39] there were not significant differences, and in 4 studies[30,33,38,40] they were significantly better in the eccentric-group.

Strength was assessed differently in 9 studies[30–32,34–37,39,41], distinguishing: strength[30,31], grip strength[32,36], isometric strength[39,41], pain-free grip strength[34,35,37] and pain-free isometric strength[34]. Tyler[30] assessed it in various forms: during wrist extension, middle-finger extension and in combination. Significant within-group improvements were observed in the eccentric-group during wrist extension and combination strength ($p<0.05$), but not during middle-finger extension ($p>0.05$); in terms of inter-group changes, they were only significantly better in the eccentric-group during combined strength ($p=0.01$), not having differences during wrist and middle-finger extension. The changes found by Peterson[31] were significantly better in the eccentric-group, both within-group and inter-group ($p<0.05$). Grip strength was assessed in 2 studies. Svernlöv[32] found improvements significantly better in the

eccentric-group, both within-group and inter-group ($p<0.01$ and $p<0.05$ respectively). Wen[36] did not find significant differences between groups. Other 2 studies evaluated the isometric strength. Maenhout[39] found significant within-group changes in the eccentric-group ($p<0.05$); in terms of inter-group changes, no significant differences were observed, except in isometric strength at 90º of shoulder abduction, where changes were significantly better in the eccentric-group ($p=0.033$). Struyf[41] did not find any within-group changes (both in eccentric-group and non-eccentric group) nor inter-group. Concerning pain-free grip strength, the 3 studies[34,35,37] showed significant within-group changes in the eccentric-group ($p<0.05$); in terms of inter-group changes, they were significantly better in the non-eccentric group in 1 study[37] (Cyriax massage and Mill's manipulation), no significant between groups in other[35], and significantly better in the eccentric-group in another one ($p=0.025$)[34]. Söderberg[34] also studied the pain-free isometric strength, finding significantly better improvements in the eccentric-group at the end of the treatment, both within-group and inter-group ($p=0.0001$). However, they were not significant in the middle of the study period.

Eccentric exercise regimens may vary from one study to another seeking for the best result. Table 2 lists the treatment variables used by authors treating impingement and epicondylar tendinopathy. The most common treatment protocol among these studies were established by Alfredson[42], which consisted of 3 sets of 15 repetitions performed twice daily. Most authors of the selected articles did not deviate much from Alfredson´s protocol. The total number of repetitions per exercise never exceeded the original 45, twice a day, by Alfredson. Additional file 1 includes the supplementary information extracted.

There is strong evidence for the utility of EE as a therapeutic tool. There is strong evidence supporting the role of EE in treating patients with epicondylar tendinopathy and shoulder impingement. There is strong evidence that EE can produce improvements for the outcomes pain, functional status and strength in most of the studies

iv. Discussion

Our systematic revision focused on the study and search for evidence about the effectiveness of the eccentric exercises for the treatment of upper limb tendinopathies. The main finding was the existence of randomized trials only for two tendinopathies: shoulder impingement and epicondylar tendinopathy. Those studying other tendinopathies, such as De Quervain´s tenosynovitis, had a low level of evidence (case series, case reports, e.g.) and were not included.

In terms of methodological quality, it was generally adequate, with only 2 studies[32,36] scoring less than 5 points on the PEDro score. Evaluators blinding was generally accomplished, with only 2 studies[31,39] in which the blinding was not respected, and other 2 studies[32,35] in which both blinding and evaluator independence were not referred.

In most of the studies, the number of included participants was enough, which was previously determined by statistical estimations. Struyf[41] included 20 participants, although a minimum of 46 participants was estimated as necessary to be significant; however, the power of the study was strong enough (80%). Wen[36] and Viswas[33] did not estimate previously the sample size, even though it could be insufficient (n=14 and n=10 respectively).

Regarding the post-treatment follow-up, 7 studies[30,33–35,38–40] did not performed it, complicating the collection of long-term results. This may influence even more in those short-term studies, in which the duration constitute a limitation itself, probably conditioning the improvement of the tendinopathy. Martinez-Silvestrini[35] developed a 6-weeks study with no post-treatment follow-up; despite both groups improved significantly, no inter-group changes were found, probably due to the short duration of the study period. Nagrale[37] developed a 4-weeks follow-up, maybe insufficient due to the short duration of the study period (4 weeks). All of this, together with the characteristic “vicious cycle” of the tendon injury[43], may limit considerably the collection of faithful and closer information to the tendinopathy reality.

Other aspects, such as the supervision of the exercises in some studies (home programmes) may constitute a limitation in its development. Six studies[31,32,34,35,39,40] based

their strengthening programme on exercises to be performed at home, may not have been a proper accomplishment or an adequate technique. Martinez-Silvestrini[35] revised the participants' technique personally at first and sixth week; moreover, they were called by telephone 2 weeks after the start of the treatment to ensure that they felt comfortable with the required technique and the intensity of the exercises, telling them also to write an "exercise diary", which was presented by all participants but one, who dropped the study. Holmgren[40] affirmed that, being home exercises, they should be few and simple to favour the adherence to treatment, as the lack of time of some participants should be considered; in addition, regular visits should be carried out by the physiotherapist.

Whether or not eccentric exercises should be performed with pain remains unclear. Six studies[30,31,33,36,37,40] developed eccentric exercises letting the pain play its role, and other 6 studies[32,34,35,38,39,41] did not permit pain during the execution of the exercises; however, positive results can be found in both cases. Martinez-Silvestrini et al.[35] took their previous clinical experience into account to decide that exercises should be pain-free; according to them, the compliance of the exercises may decrease when patients experience pain, worsen this situation whether they are not supervised and probably losing the correct technique. Söderberg[34] developed a diary exercise programme to be performed without pain; in this case, the fact that the exercises were planned to be done every day may justify the pain-free point, in order to allow an adequate post-session recovery and not to limit the participants physically for future sessions.

Regarding inclusion method, Peterson[31] recruited the participants by doctors and physiotherapists referral, and also with newspaper advertisements so that people with potential tennis elbow symptoms could participate in the study. Although this was not a random population sample, it may be regarded as fairly representative of this type of patient in the general population. Holmgren[40] recruited the participants who were in a waiting list for surgery; this could limit the validity of the study, although it is believed that, in spite of everything, the sample could be representative.

The lack of general agreement with respect to inclusion and exclusion criteria may lessen the validity of the studies. Svernlöv[32], Viswas[33], Söderberg[34] and Nagrale[37] set the pain at palpation of the epicondyle as a inclusion criteria; the individual participantivity in palpation skills may have lead the inclusion process to error.

The failure to accurately report exercise protocols and the substantial variation in exercise parameters made it difficult to assess the effectiveness of each study's ability to isolate an eccentric exercise component and provide a progressive muscle stimulus. There is still a controversy in the literature for the ideal parameters of the eccentric exercise protocols. The number of sets and repetitions, as well as the number of sessions per week and the resting time between sets, vary from one study to another. In a similar vein, eccentric treatment is combined with other therapeutic modalities in most of the studies, such as stretching, massage, ultrasound, orthotic devices, etc. Consequently, the attempt to isolate the results and evaluate only the effect of the eccentric exercises becomes complicated.

v. Conclusion

Eccentric exercises are effective for upper limb tendinopathies, but its superiority against other methods is not totally clear. Further studies with higher level of evidence on other tendinopathies and areas of the upper limb are needed.

Methodological quality such as the number of participants included was generally adequate in all of the studies. However, the lack of general agreement regarding inclusion and exclusion criteria may lessen the validity of the studies.

Long-term studies and longer follow-up periods become imperative, as well as more studies with supervised exercises programmes in order to fight the possible non-adherence to treatment, and also to determine the most correct parameters of the eccentric exercise protocols and the inclusion or not of pain during its execution.

vi. Practical implications

- Eccentric exercise is likely a useful treatment for upper extremity tendinopathies, but whether it is more or less effective than other forms of therapeutic exercise is unclear.

- Eccentric exercise may be more effective in treating upper extremity tendinopathies than any other conservative form of treatment, but it may need to be combined with an adequate managament of the stressful stimulus for the best outcome.

- Future research should recruit sufficient numbers of subjects and use valid, and reliable clinical and functional outcome measures to evaluate the role of eccentric exercise in treating upper extremity tendinopathies.

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viii. Conflicts of interest and funding

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x. Tables

Table 1. Synopsis of the included studies.

Table 2. Components and parameters of the eccentric strengthening protocols.

x. Tables

Table 1. Synopsis of the included studies

Main autor (year)	Pathology	Previous duration of symptoms	Intervention		Outcome (95% CI)					Post-treatment follow-up	PEDro Score
			Experimental Group (EG)	Control Group (CG)		Experimental Group		Control Group			
						Baseline	FFU	Baseline	FFU		
Tyler et al (2010)[30]	Epicondylar tendinopathy	6 weeks minimum	≈ 7 weeks isolated eccentric exercise, as well as stretching, US, deep transverse massage, heat and ice. Exercises and stretching were also prescribed as home exercises (n=11)	Same as EG, but with isotonic exercises instead of eccentric exercise. Exercises and stretching were also prescribed as home exercises (n=10)	DASH (0-100) ‡ VAS (0-10) ‡ Strength (*Lafayette Manual Muscle Tester* dynamometer): - Wrist extension deficit (%) ¥ - Middle finger extension deficit (%) ¥ - Combined strength deficit (%) ‡ Tenderness (dynamometer attachment) (%) ‡	38 ± 29 6.7 ± 2.8 30 ± 11% 17 ± 24% 24 ± 15% 51 ± 26%	9 ± 21 (p=0.002) 1.3 ± 2.7 (p=0.0001) 9 ± 23% (p=0.005) 1 ± 33% (p=0.18) 5 ± 20% (p=0.03) 15 ± 33% (p=0.005)	38 ± 30 6.3 ± 2.8 28 ± 19% 12 ± 22% 20 ± 16% 40 ± 28%	33 ± 22 (p=0.33) 4.9 ± 2.7 (p=0.015) 21 ± 25% (p=0.43) 13 ± 31% (p=0.84) 17 ± 18% (p=0.36) 38 ± 34% (p=0.82)	None	6
Peterson et al (2014)[31]	Epicondylar tendinopathy	>3 months	3 months eccentric exercise at home (n=60)	Same as EG, but with concentric exercise instead of eccentric exercise (n=60)	VAS (0-100): ¥ - During maximum voluntary contraction - During maximum muscular elongation Strength, in Newton (dinamómetro de agarre manual *Chatillon MSE 100*) ‡	47.9 ± 26.8 40.6 ± 27 119.9 ± 44.1	9.8 ± 19.5 (p<0.001) 4.7 ± 12.4 (p<0.001) 128.8 ± 50 (p<0.05)	46.1 ± 27.5 38.8 ± 28.6 133.7 ± 48.4	12.8 ± 24.8 6.6 ± 18.9 138.3 ± 49.3	9 months	6

					DASH (0-100) ¥	28.8 ± 18.4	9.6 ± 17.8	27.5 ± 17.3	9.6 ± 16.3		
					GQF: ¥						
					- Activiy	28.4 ± 6.9	24.9 ± 7.6	27.4 ± 7	23 ± 7.4		
					- Well-being	5.3 ± 1.5	5.1 ± 1.6	5.5 ± 1.4	5.4 ± 1.3		
					- Complaints	6.6 ± 5.8	4.2 ± 5.5	6.3 ± 4.9	4.9 ± 6.1		
Lombardi et al (2008)[38]	Shoulder impingement	≈14 months	8 weeks muscular strengthening programme, both concentric and eccentric (n=30)	8 weeks on a waiting list (n=30)	VAS (0-10): ‡					None	8
					- During rest	4.2 ± 2.4	2.4 ± 2.1 (p=0.001)	3.9 ± 2.6	4.3 ± 3.2		
					- During movement	7.4 ± 1	5.2 ± 2 (p=0.002)	7.1 ± 1.5	7.1 ± 2.5		
					DASH2 (0-100) ‡	49.6 ± 23.5	28.7 ± 24.8 (p=0.032)	47.4 ± 24.7	44.2 ± 28.2		
					DASH3 (0-100) ‡	44 ± 17.6	33.2 ± 18.7 (p=0.046)	44.8 ± 18.3	43.4 ± 22.8		
					SF-36 (0-100): ‡						
					- Physical function	54.8 ± 19.8	64.3 ± 19	62.2 ± 20.3	62.8 ± 22.3		
					- Physical role limitation	31.7 ± 37.1	36.7 ± 41.4	25.8 ± 36.2	30.8 ± 39.8		
					- Pain	43.3 ± 17.3	54.3 ± 16	43.9 ± 19.2	46.7 ± 24.1		
					- General health	73.4 ± 17.2	73.9 ± 20.3	70.5 ± 25.6	68.2 ± 25.3		
					- Vitality	52.4 ± 24.1	54.8 ± 24.7	50.4 ± 25.4	49.4 ± 26.9		
					- Social function	69.6 ± 32.3	76.7 ± 27.4	73.3 ± 29.7	65.4 ± 27.2		
					- Emotional role limitation	40 ± 40.5	62.2 ± 40.8	54.4 ± 44.2	55.5 ± 42.3		
					- Mental health	53.5 ± 24.9	62.9 ± 22	54.9 ± 25.1	56.5 ± 25.1		
					Shoulder ROM (goniometry):						
					- Flexion ¥	126.7 ± 24.4	137.1 ± 24.8	119.5 ± 29	130.6 ± 27.4		
					- Abduction ‡	116.8 ± 24.5	136.9 ± 28.5	129.7 ± 31.5	127.2 ± 31.6		
					- Internal rotation with 90º shoulder abd ¥	40 ± 14.9	45.3 ± 13.3	33.2 ± 16	35.6 ± 15.7		
					- External rotation with 90º shoulder abd ¥	75.6 ± 19.8	82.7 ± 18	67.5 ± 29.7	70.5 ± 31.7		
					- External rotation with arm alongside the body ¥	61.9 ± 15.9	65.4 ± 13.9	60.1 ± 16.6	64.8 ± 18.4		
					- Extension ‡	48.2 ± 8.7	54.5 ± 8.8	44.8 ± 12.5	46.9 ± 12.2		
					Isokinetic evaluation of the shoulder at a						

					speed of 60º/sec (*Cybex 6000* dynamometer): ¥ - Flexion (Peak Torque/Total Work) - Extension (Peak Torque/Total Work) - Abduction (Peak Torque/Total Work) - Adduction (Peak Torque/Total Work) - Internal rotation (Peak Torque/Total Work) - External rotation (Peak Torque/Total Work)	 25.5±12.82 / 32.5±17.27 36.6±19.25 / 49.87±28.2 22.1±11.89 / 23.87±17.68 29.2±17.49 / 29.7±24.26 19.83±8.06 / 24.7±11.97 11±4.95 / 12.73±6.94	 29.2±11.46 / 37.73±17.57 40±18.42 / 55.37±29.11 24.37±12 / 25.53±17.78 33.8±18.39 / 33.67±25.94 22.23±9.28 / 28.93±13.03 12±5.12 / 17.37±14.85	 22.3±10.7 / 27.6±16.26 30.23±17 / 42.17±24.63 16.63±11.9 / 18.43±16.41 21.1±16.86 / 23.9±22.38 16.7±7.5 / 19.9±9.5 9.2±3.53 / 10.53±5.22	 22±13.46 / 28.23±20.41 28.4±19.27 / 37.93±27.29 15.8±11.44 / 16.27±16.18 21.73±18.4 / 22.6±24.63 17.13±7.99 / 20.3±10.68 9.53±4.15 / 12±7.52		
Svernlöv et al (2001)[32]	Epicondylar tendinopathy	≈10 months	12 weeks eccentric exercise (*Curwin & Stanish* modified programme, 1984) at home (n=15)	12 weeks contraction-relax-stretching exercises at home (n=15)	VAS: ¥ - During rest - While palpating the epicondyle - During resisted wrist extension - Middle finger test - Grip strength test	At the beginning, higher VAS result in EG than in CG (p<0.04). After 3 months, no significant differences between groups. Significant improvement in 4 out of the 5 VAS, except during rest. After 6 months, 14 subjects referred a complete pain relief. Grip strength increased significantly after 3 months (p<0.001); after 6 months, improvement was significantly better in EG (p<0.05)		In CG, significant improve in 4 out of the 5 VAS, except assessing grip strength. After 6 months, 13 subjects referred a complete pain relief. Grip strength increased significantly after 3 months (p<0.001)		9 months	4
					Grip strength (effort gauge device) ‡	54.8 (33.9 - 83.2)	66 (43 - 92.3)	45.3 (28.6 - 71.8)	54.6 (35.3 - 89.9)		
Viswas et al (2012)[33]	Epicondylar tendinopathy	Between 8 and 10 weeks	4 weeks supervised exercise (stretching and	4 weeks physiotherapy based on Cyriax	VAS (0-10) ‡ TEFS ‡	7.9 33.2	4.3 23.9	7.9 33.2	5.6 25.8	None	6

			eccentric exercises) (n=10)	massage and Mill´s manipulation (n=10)							
Maenhout et al (2013)[39]	Shoulder impingement	3 months minimum	12 weeks traditional treatment (internal and external shoulder rotation with Thera-Band®) and heavy load eccentric exercise, both at home (n=31)	Same as EG, but without heavy load eccentric exercises (n=30)	Isometric strength (with HHD): - Isometric strength at 0º abd ¥ - Isometric strength at 45º abd ¥ - Isometric strength at 90º abd ‡ - Isometric strength at external rotation ¥ - Isometric strength at internal rotation ¥ SPADI (0-100) ¥ Subjective perception of improvement (i*n number of subjects/group*): ¥ - 0 (no change) - 1 (very little improvement) - 2 (little improvement) - 3 (some improvement) - 4 (large improvement) - 5 (very large improvement) Total subjects	 127.9 ± 27.6 71.2 ± 12.3 64.7 ± 12.6 82.9 ± 12.5 121.7 ± 17.9 42 ± 11 n=2 n=0 n=3 n=11 n=14 n=0 n=30	 154.3 ± 27.6 (p=0.005) 81.6 ± 12.2 (p=0.001) 78 ± 12.5 (p<0.001) 96 ± 12.4 (p<0.001) 129 ± 17.9 (p=0.038) 17 ± 11.4 (p<0.001) n=0 n=1 n=3 n=9 n=9 n=5 n=27	 123.2 ± 28 68.2 ± 12.3 63 ± 12.7 83.4 ± 12.9 119 ± 18.2 44.3 ± 11.5 n=2 n=4 n=4 n=7 n=9 n=1 n=27	 147.1 ± 27.2 (p<0.001) 83.5 ± 11.8 (p<0.001) 70 ± 12.2 (p>0.05) 92.7 ± 12.3 (p=0.002) 125 ± 17.2 (p=0.006) 14.5 ± 11.7 (p<0.001) n=0 n=0 n=2 n=5 n=9 n=4 n=20	None	6
Holmgren et al (2012)[40]	Shoulder impingement	>6 months	12 weeks stretching, eccentric and concentric exercises, as well as home exercises (n=51)	12 weeks unspecific mobility exercises for the neck and shoulder, also with home	*Constant-Murley* score (0-100) ‡ DASH (0-100) ‡ VAS (0-100): - During rest ¥ - During activity ¥	48.5 ± 15 30 ± 14 15 ± 19 61 ± 22	72.5 ± 19 16 ± 15 10 ± 14 25 ± 26	43.5 ± 15 35 ± 19 20 ± 21 66 ± 20	52.5 ± 23 29 ± 19 20 ± 25 41 ± 27	None	7

				exercises (n=46)	- At night ‡ EQ-5D (-0.59 – 1) ‡ EQ VAS (0-100) ¥	46 ± 28 0.67 ± 0.23 68 ± 15	15 ± 22 0.82 ± 0.14 75 ± 20	40 ± 30 0.62 ± 0.23 62 ± 20	27 ± 27 0.69 ± 0.24 69 ± 21		
Söderberg et al (2012)[34]	Epicondylar tendinopathy	1 month minimum	6 weeks using a forearm band, warming-up exercises for wrist extensors and eccentric exercises at home (n=18)	Same as EG, but without eccentric exercises (n=19)	Pain-free grip strength (*Martin* vigometer, in kPa) ‡ Pain-free isometric strength in wrist extensors (*Nicholas myometer*, in kg) ‡ VAS (0-100) ¥	At mid-term of the study (3 weeks), no significant effect was found for grip strength (p=0.300) or isometric extensors strength (p=0.976). However, at the end (week 6), EG subjects improved significantly in both facets (p=0.025 and p=0.0001 respectively). Regarding pain, both groups improved significantly (in EG, p=0.001; in CG, p=0.005), although inter-group analysis did not show significant differences at week 3 (p=0.869) or at the end of the study (p=0.916). In EG, the proportion of cases with lateral epicondilalgia decreased from 100 to 44% (8/18), whereas in CG was from 100 to 79% (15/19)				None	6
Martinez-Silvestrini et al (2005)[35]	Epicondylar tendinopathy	>3 months	In this 6 weeks follow-up study, subjects were allocated in 3 groups: stretching and other conservative therapies ("stretching group", n=33), stretching and concentric exercises programme ("concentric group", n=30), and stretching and eccentric exercises programme ("eccentric group", n=31), all of these as home programmes. Out of total 94 subjects at the beginning, 81 completed the 6 weeks follow-up study: 28/33 in the "stretching group", 26/30 in the "concentric group" and 27/31 in the "eccentric group"		Pain-free grip strength (dynamometer) ¥ - Stretching group - Concentric group - Eccentric group PRFEQ: ¥ - Stretching group - Concentric group - Eccentric group DASH (0-100): ¥ - Stretching group - Concentric group - Eccentric group SF-36 ¥ VAS (0-100): ¥ - Stretching group - Concentric group - Eccentric group	**Baseline** 23 ± 15 17 ± 9.7 22 ± 12 3.7 ± 1.7 3.8 ± 1.7 3.3 ± 1.5 27 ± 14 26 ± 13 25 ± 13 Changes before and after the study were significant (p<0.01), as it occurs with the rest of the results 48 ± 21 49 ± 21 46 ± 20	**FFU** 30 ± 17 (p<0.01) 25 ± 12 (p<0.01) 26 ± 14 (p<0.01) 1.5 ± 1.6 (p<0.01) 1.3 ± 1.8 (p<0.01) 1.2 ± 1.7 (p<0.01) 15 ± 14 (p<0.01) 17 ± 14 (p<0.01) 16 ± 15 (p<0.01) Changes before and after the study were significant (p<0.01), as it occurs with the rest of the results 25 ± 24 (p<0.01) 35 ± 25 (p<0.01) 24 ± 24 (p<0.01)	None	6

Wen et al (2011)[36]	Epicondylar tendinopathy	4 weeks minimum	14 weeks eccentric exercise (n=14)	14 weeks local modality treatments, iontophoresis, US, stretchings (n=14)	VAS (0-100) ¥ Grip strength ¥ General satisfaction ¥	At the beginning, VAS score in EG was 63±19, whereas in CG was 61±19. At week 4, pain in EG decreased significantly an average of 34 points (p=0.01), and 28 points in CG (p<0.01). No significant inter-group differences were found at any point of the evaluations (start, week4, week8, week12, week16 and week 20), except at week 8, when the EG had a significant pain relief, better than in CG (p<0.01) No significant inter-group differences were found at any point of the evaluations No significant inter-group differences were found at any point of the evaluations (p=0.84)				6 weeks	3
Struyf et al (2013)[41]	Shoulder impingement	30 days minimum	4-8 weeks manual mobilizations, stretching and motor control training of the scapula, also at home (n=10)	4-8 weeks eccentric exercise, manual therapy (passive mobilizations, friction massage) and US, as well as home exercise (n=10)	SDQ (0-100) † VNRS (0-10): - Hawkins ¥ - *Empty can* ¥ - Neer † VAS (0-10): † - During rest - During movement Isometric strength (in Newtons) ¥ PMI ¥ Upward scapular rotation, in degrees (inclinometer): ¥ - 0º of shoulder abduction - 45º of shoulder abduction - 90º of shoulder abduction - 135º of shoulder abduction	55.9 ± 14.6 5 ± 1.8 4.2 ± 2.9 5.3 ± 2.7 2.8 ± 2.8 5.7 ± 2.6 51.36±15.79 9.1 ± 2.3 -9.4 ± 3.7 -3.5 ± 4.5 4.9 ± 7 12.5 ± 9	35 ± 14 (p=0.006) 2.9 ± 2.2 (p=0.017) 1.9 ± 2 (p=0.003) 3.1 ± 3.1 (p=0.009) 1.3 ± 1.5 (p=0.264) 3 ± 1.9 (p=0.004) 55.79±18.71 (p=0.542) 10.3 ± 0.7 (p=0.472) -9.6 ± 2.6 (p=0.895) -5 ± 4.1 (p=0.554) 1.4 ± 3 (p=0.119) 9 ± 5.4 (p=0.218)	50.9 ± 11.9 3.9 ± 3.4 3.8 ± 3.6 5.1 ± 3.6 2.4 ± 2.5 6.3 ± 1.9 62.9±20.75 8.9 ± 1.2 -11.1 ± 8.1 -4.9 ± 5.4 2.3 ± 5.4 8.7 ± 9.2	48.7 ± 11.3 (p=0.725) 3.9 ± 3 (p=0.815) 3 ± 2.8 (p=0.566) 6 ± 2.1 (p=0.451) 2.3 ± 2.6 (p=0.705) 5.1 ± 2 (p=0.111) 74.11±34.28 (p=0.419) 9.2 ± 0.5 (p=0.388) -9.6 ± 4.6 (p=0.481) -7 ± 6.5 (p=0.434) 0.6 ± 4 (p=0.193) 6.1 ± 3.9 (p=0.287)	12 weeks	8

					- Maximum shoulder abduction Acromion-to-bed distance (supine, vertical measurement with the *Manutan*™ calibrator, in cm): ¥ - Relaxed - Retracted	19.4 ± 12.7 0.42 ± 0.06 0.31 ± 0.06	19.3 ± 10 (p=0.965) 0.4 ± 0.05 (p=0.386) 0.3 ± 0.05 (p=0.703)	14.4 ± 9.6 0.42 ± 0.07 0.34 ± 0.07	10.6 ± 11.3 (p=0.340) 0.46 ± 0.05 (p=0.082) 0.32 ± 0.06 (p=0.099)		
Nagrale et al (2009)[37]	Epicondylar tendinopathy	≈14 weeks	4 weeks Cyriax treatment and Mill´s manipulation (n=30)	4 weeks phonophoresis and supervised exercise (stretching and eccentric exercises) (n=30)	VAS (0-10) † Pain-free grip strength, in lbs (dynamometer) † TEFS (0-40) ¥	8.2 16.53 33.66	3.16 (p<0.05) 42 (p<0.05) 12.73 (p<0.05)	8.1 17.33 33.1	5.6 (p<0.05) 28.26 (p<0.05) 21.2 (p<0.05)	4 weeks	6
	FFU: Final Follow-Up; ROM: Range Of Motion; *DASH*: *Disabilities of the Arm, Shoulder and Hand*; *DASH2: Disabilities of the Arm, Shoulder and Hand optional module 2*; *DASH3: Disabilities of the Arm, Shoulder and Hand referent of 30 questions*; *VAS: Visual Analogue Scale*; *SF-36: Short-Form 36; TEFS: Tennis Elbow Function Scale; PMI: Pectoralis Minor Index* [(length/height)x100]*; HHD: Hand-Held Dynamometer; SPADI: Shoulder Pain And Disability Index; GQL: Gothenburg Quality of Life; PRFEQ: Patient Rated Forearm Evaluation Questionnaire; SDQ: Shoulder Disability Questionnaire; VNRS: Verbal Numeric Rate Scale; EQ-5D and EQ-VAS are part of EuroQol instrument* *‡: significantly better changes in eccentric-group; †: significantly better changes in non-eccentric group; ¥: no significant differences between groups*										

Table 2. Components and parameters of the eccentric strengthening protocols

Main author (year)	Description of the eccentric exercise	Frequency per week	Duration (weeks)	Sets (rest)	Reps	Progression of the intensity
Tyler et al (2010)[103]	Use of elastic band Thera-Band®, which was twisted using wrist flexion of the uninvolved limb, slowly allowed untwisting by eccentric wrist extension with the involved limb. Each contraction lasted approximately 4 seconds	1.4 average (9 sessions in total)	≈7	3 (30 seconds rest between sets)	15	Whether the patient did not refer pain or discomfort during the exercise, the elastic band was changed for a thicker one
Peterson et al (2014)[104]	Subjects sitting on a chair, forearm pronated on the armrest or on an adjacent table, holding the handle of the plastic water can with a clenched fist in pronation and the container hanging freely in front of the armchair or below the tabletop. Then, eccentric flexion of the affected wrist, lowering the weight and lifting it back again with the unaffected arm	7 (1time/day)	12	3	15	Initial weight was 1kg (1 litre of water) for women and 2kg for men. Weekly, the weight was increased 1 hectogram (1 decilitre of water)
Lombardi et al (2008)[111]	The patients used a repetition maximum exercise in which they performed 6 repetitions with the maximum bearable weight, thereby determining the 6 repetition maximum (6RM). Multipulley muscle-building equipment was used for the exercises. To strengthen the flexors of the shoulder, the patient was positioned with his or her back to the equipment and the elbow flexed at 90º,	2	8	2 (2min rest between sets)	8	First set was performed with 50% of the 6RM, and the second with 70% of the 6RM. Every other week, the 6RM was re-evaluated. The exercise was interrupted if the patient felt pain and performed another movement

	performing the flexion movement from 0º to 90º. For the extensors, the patient faced the equipment with the elbow flexed at 45º and the shoulder at 60º of flexion and 30º of extension. For the medial and lateral rotators, the patient was positioned alongside the equipment with the elbow flexed at 90º: for the medial rotation, the patient started at 45º of lateral rotation and moved to 45º of medial rotation; for the lateral rotation, the patient began at 45º of medial rotation and moved to 3º of lateral rotation. The speed of movement was 2 seconds for both the eccentric and concentric phases					
Svernlöv et al (2001)[105]	Experimental group programme: 1-Warm-up of the forearm extensors and flexors with wrist movements without any load (2-3min) 2-Static stretch (15-30 seconds, 3-5 times) 3-Eccentric exercises of the forearm extensors muscles (10 seconds). Subject in sitting position, elbow in 90º of flexion resting on a table, holding the dumbbell over the edge of the table 4-Static stretch, as prior to exercise. To be performed once daily Eccentric exercises were intended to be pain-free. In addition, the subjects used an elbow band (counterforce brace) during activity and a wrist support at night	7 (1 time/day)	12	3	15	Initial weight: 1 kg (men), 0.5 kg (women). 10% weight increase weekly

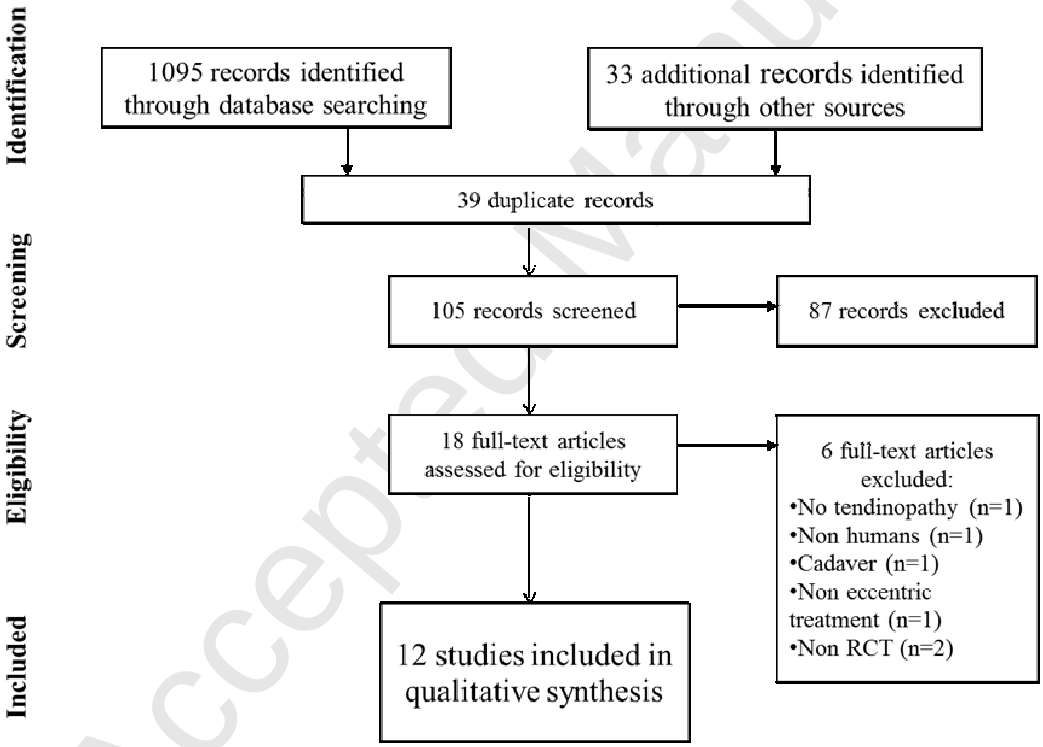
Viswas et al (2012)[106]	Subjects in sitting position, with full elbow extension, forearm pronation and maximum wrist extension. From this position, the patient slowly lowered wrist into flexion for a count of 30, using the contralateral hand to return the wrist to maximum extension. Patients were instructed to continue the exercise even when they experienced mild discomfort and to stop it if the pain worsened and become disabling	3	4	3 (1 min rest between sets)	10	For whom the eccentric exercise could be performed without minor discomfort or pain, the load was increased using free weights based on the patients 10 RM
Maenhout et al (2013)[112]	Subjects performed a full can (thumb up) abduction in the scapular plane with a dumbbell weight at a speed of 5 seconds/repetition, twice a day. Starting position of the eccentric phase at full scapular abduction had to be pain free and, if not, patients were advised to stretch out the arm at a slightly lower degree of scapular abduction	1time/week the first 6 weeks, and 1 time/2weeks the last 6 weeks	12	3	15	Conditions: - During the last set, pain should be more than resting, but no more than a score of 5/10 on the VAS - Pain after the exercise should not exceed 5 on the VAS and should have subsided the following morning - Pain should not increase from day to day Whenever the pain was no longer present during the last set, dumbbell weight was increased with 0.5 kg
Holmgren et al (2012)[113]	Experimental group programme: -2 eccentric exercises for the rotator cuff -3 concentric/eccentric exercises for the scapula stabilisers -1 posterior shoulder stretch The strengthening exercises were performed in a determined number of sets and repetitions (see corresponding column). Patients were	7 → 2times/day the first 8 weeks, 1time/day from week 8 to 12	12	3	15	The exercises were individually adjusted and progressed with increased external load by using weights and elastic rubber band at the physiotherapist visits once every other week during the whole rehabilitation period. The patients were not allowed to exceed 5/10 on the VAS

	recommended to feel some pain during loading. After completion of an exercise session, increased pain had to revert to levels before exercise before the next					
Söderberg et al (2012)[107]	With the elbow flexed 70º, subjects seated on a chair with the forearm pronated resting on a table, with the wrist and hand over the edge and holding a bucket of water. They were instructed to place the non-affected hand over the one holding the bucket and slowly lift it with the non-affected hand, thus avoiding the concentric phase in the affected arm. With the affected hand extended, the subjects removed the unaffected hand slowly and then, counting to 3, lowered the hand to cause a flexion hand movement. They were told to adjust their resisted weight so that they were able to perform the prescribed repetitions during pain-free intervals and, if not, the weight would be decreased	7 (1time/day)	6	2	8-12	The first week, they performed 2 sets of 8-12 reps, 1 time/day. For the next two weeks, the progression would be twice/day. From the third week, they would perform 3 sets of 8-12 reps, twice/day
Martinez-Silvestrini et al (2005)[108]	Subjects in a sitting position, elbow flexed and forearm pronated resting on the thigh, with the hand hanging over the knee, holding the resistance band, which was fixed on the floor with the ipsilateral foot. With the non-affected hand, subject pulled up the band, lengthening it, in order to make it lax and allow the affected hand to perform	7 (1time/day)	6	3 (2-5 min descanso entre sets)	10	The appropriate resistance band (light, medium, or heavy) was determined by a 10-repetition trial. The length of the band was adjusted so that it was somewhat difficult to perform 10 repetitions. During the initial trial, the length of the band was marked with a permanent ink marker to avoid variability of resistance between

	a wrist extension. Then, the band was slowly lowered from full wrist extension to full wrist flexion					sessions. Those who performed the repetitions easily without increasing pain, resistance was increased by shortening the band in 1-inch increments from the initial length mark
Wen et al (2011)[109]	Elbow and wrist of the affected extremity in extension, with forearm pronated resting on a table, with the hand and wrist over the edge. The other hand pushed the affected hand to wrist flexion for 6-8 seconds, while the affected resisted the force performing an extension	2 (first 2 weeks) and 1 (for 12 weeks)	14	3	15	Initial resistance applied by the non-affected hand had to be bearable during 3 sets of 15 repetitions. As the pain tolerance increased, more resistance was applied
Struyf et al (2013)[114]	Subjects in a standing position, holding the elastic MSD-Band with the affected extremity, they performed shoulder flexion, extension, internal and external rotation. Subjects were asked to quickly move in the desired direction and consequently slowly returning to the starting position. Home exercises were the same that they did during the supervised therapy session, also with the elastic MSD-Band	Between 1-3 (depending on the subject), for a total of 9 sessions	Between 4 and 8 weeks (depending on the subject)	3 (2 min rest between sets)	15	Load was increased in terms of gravity, ROM, number of repetitions, speed and resistance. Whether the subjects could not correctly perform the exercise or pain was experimented, the load was not increased
Nagrale et al (2009)[110]	Subjects in a sitting position, with the forearm pronated, elbow and wrist fully extended. From this position, they slowly lowered the wrist to flexion, counting to 30, using the other hand to return the affected to the starting	3	4	3 (1 min rest between sets)	10	When the exercise was performed without the minimum pain or discomfort, the load was increased using dumbbells, based on the top bearable load of each subject in 10 repetitions
Reps: *repetitions*; *VAS*: *Visual Analogue Scale*; *ROM*: *Range Of Motion*; *RM: Repetition Maximum*						

xi. Figure legends

Figure 1. Flow chart of the Selection Process according to PRISMA Statement. According to: *Moher D, Liberati A, Tetzlaff J, Altman DG. & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg Lond Engl 2010; 8: 336-41.*



Conflict of interest

The authors declare that no actual or potential conflict of interest exists.

Author´s contributions

MO contributed to study design, data extraction, evidence synthesis, and editing, reviewed the study protocol, made suggestions that improve the design, incorporated all feedback and drafted the manuscript.

IM conceived, coordinated and designed the study, contributed to data extraction, evidence synthesis, and editing, and helped draft the manuscript.

All authors have read and approved the final manuscript.

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