The effect of dose on resistance exercise therapies for tendinopathy: A systematic review and meta-analysis protocol.

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DOI: 10.31236/osf.io/an3j6

SportsRxiv hosted preprint version 1

Last updated

PREPRINT - NOT PEER REVIEWED

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Funding

This project is funded by the National Institute for Health Research (NIHR) [Health Technology Assessment (HTA) 129388 Exercise therapy for the treatment of tendinopathies]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Conflicts of interest

The authors declare no conflict of interest.

1.0 Introduction

Tendinopathy is a common musculoskeletal condition associated with degenerative changes within a tendon affecting both athletic and non-athletic populations.¹ The condition is characterized by a combination of pain,¹ and impaired movement² and function³, requiring extended periods for recovery.^{2,4,5} Tendinopathy can affect any muscle-tendon unit in the body,⁶ however, it is most frequently reported in the Achilles, patellar, lateral elbow, rotator cuff, and hip tendons.⁶ Surveys of prevalence of lower extremity tendinopathy in the general population have reported rates of 11.8 and 10.5 per 1000 person-years,⁷ whilst prevalence for upper limb tendinopathies have been estimated between 1.3% to 21.0%.⁸⁻¹⁰ Tendinopathies can affect children, adolescents, and adults of all ages, and many tendinopathies have a chronic or recurrent course.⁶ Costs to the individual, the health service and economy (due to absenteeism and loss of productivity) are substantial such that identifying effective interventions is a priority. Musculoskeletal conditions including tendinopathies also have a substantive influence on primary and secondary healthcare use.¹¹ By identifying effective interventions across a range of tendinopathies, General Practitioners and other first-contact practitioners (e.g. physiotherapists) can be confident in delivering effective evidence-based practice. With an ageing population, and increasing pressure and demands on healthcare services, the need for clear guidance for evidence-based practice has never been more important.

Exercise therapy is the mainstay of conservative management of tendinopathy and has focused largely on resistance training, and in many instances eccentric strengthening techniques, to date.¹² The objective with exercise therapy is to encourage load tolerance that leads to structural adaptation at the musculotendinous unit and restores function.¹³⁻¹⁴ Isometric, isotonic, and heavy slow resistance training have also been recommended for some tendinopathies (e.g. patellar) with suggested efficacy.¹⁵ The effectiveness of exercise therapy is likely to be influenced not only by the specific exercises performed but also the magnitude of the stimulus described by the concept of exercise dose.¹⁶ At the most basic level in clinical settings, exercise dose comprises three variables including frequency, duration, and intensity, with overall exercise dose quantified as the product of all three variables.¹⁷ With an increasing evidence base of effectiveness across a range of populations and tendinopathies, it has been recommended that both primary research and evidence synthesis studies attempt to identify dose-response relationships and ultimately seek to determine optimum exercise dosages.^{16,18,19} The potential to develop dose-response relationships may be most likely for resistance exercise due to the amount of data available from primary studies and the ability to accurately quantify dose variables including intensity. Initial attempts to synthesise evidence and identify dose-response relationships were limited by setting restrictive inclusion criteria substantially reducing the amount of data available. Meyer et al.¹⁹ only included three studies when investigating the effect of eccentric exercise protocols for Achilles tendinopathy. In a similar proceeding systematic review of eccentric exercise and Achilles tendinopathy, the number of included studies was increased to eight, however, the authors still concluded that heterogenous outcomes and methodological limitations meant that data could not be pooled, nor recommendations made regarding dose-response.²⁰

Two recent approaches have been adopted in evidence synthesis research to better determine dose-response

relationships in exercise therapy for tendinopathy. In a systematic review conducted by Naunton et al.²¹, pairwise effect sizes were calculated for studies that compared exercise therapies with placebo or no treatment arms in rotator cuff related shoulder pain. The approach enabled calculation of a relative effect size metric that could be pooled for levels of an exercise dose independently (e.g. low intensity vs high intensity), and then compared with each other. Naunton et al.²¹ used this approach to compare progressive resistance exercise with non-progressive resistance exercise. The systematic review identified four studies including progressive stimuli, and four studies that maintained a constant resistance exercise stimuli. Using measures of pain as a meta-analysis outcome, clear statistical evidence was obtained for a positive effect of progressive resistance exercise with best estimates identifying decreases in pain of between 10 and 15%. In contrast, best estimates for decreases in pain were only between 1 and 3% for non-progressive resistance exercise and all confidence intervals overstretched the regions of no effect and an effect favouring control. A second approach to investigate the effects of exercise dose was adopted by Young et al.¹⁶ who attempted to increase the amount of data by including research studying multiple common disorders. The systematic review and meta-analysis included eighteen studies across interventions investigating Achilles tendinopathy, ankle sprains and planar heel pain. Several trends were identified including greater effects with increased frequency and progressive exercise as tolerated compared with pre-prescribed sets and repetitions. However, no formal statistical comparisons of exercise dose were made by Young et al.¹⁶ limiting the conclusions that can be drawn.

The purpose of the present systematic review and meta-analysis is to investigate the effect of resistance exercise dose across multiple common tendinopathies (rotator cuff, lateral elbow, patellar or Achilles) where the frequency, volume and intensity can be accurately quantified. By combining a large data set with contemporary meta-analysis and meta-regression approaches (including relevant covariates within models), the present systematic review will attempt to explore statistical heterogeneity and better assess potential dose-response relationships that may exist. Where placebo and no-treatment arms are included, these studies will be used to reduce heterogeneity and provide sensitivity analyses to support or refute analyses with larger, but more complex data.

2.0 Inclusion criteria

This review is part of a project funded by the National Institute for Health Research (NIHR); Health Technology Assessment (HTA) 129388 Exercise therapy for the treatment of tendinopathies. The inclusion criteria are influenced by the project aims, the results of our initial scoping review mapping the exercise and tendinopathy literature²² as well as stakeholder workshops.

Participants

This review will include people of any age or gender with a diagnosis of rotator cuff, lateral elbow, patellar or Achilles tendinopathy of any severity or duration. Studies that include participants with tendinopathy in the absence of full thickness or large tears, will be included. Groups where the tear size cannot be determined will also be excluded as these require different management approaches. We will accept trial authors' diagnoses where

a clearly verifiable group of clinical features is reported including: pathognomonic location of pain; a symptom altering response to applied load and/or stretch, with there being a specific test for most tendinopathies; strategies to rule out differential diagnoses; ultrasound or magnetic resonance imaging confirmation of structural change. Studies with mixed groups will have data included where there is clear reporting of the tendinopathic group, or they make up > 90% of the investigated cohort.

Intervention

The health technology being assessed is resistance exercise which can be subcategorised based on the predominant contraction mode (see appendix I for definitions). Interventions combining resistance exercise with other active therapies (e.g. laser, shockwave, manual therapy or injection) will not be included. Resistance exercise may be delivered in a range of settings (e.g. primary care, secondary care, community, people's homes) by a range of health or exercise professionals (e.g. physiotherapists, strength & conditioning coaches, personal trainers) or support workers, and may be supervised or unsupervised (i.e. self-management). No restrictions will be placed on these factors for inclusion. To be included in the review, studies are required to report sufficient information regarding the resistance exercise dose, including frequency (defined as the number of training sessions performed per week), volume (defined as the number of repetitions, sets, or repetitions multiplied by sets) and intensity (defined in absolute terms as the magnitude of the resistance used, or in relative terms either as a percentage of the maximum resistance that can be overcome for a single repetition or scaled to the maximum number of repetitions that can be completed at a given absolute load). Where sufficient information is not presented in the main text of a study to quantify all three dose variables, a search will be made of the publishers' website to check for supplementary files that may include relevant information.

Comparator

Both non-controlled (resistance exercise only) and controlled (comparator adjusted) effects will be calculated. The comparator used for controlled effects will include placebo interventions and no treatment.

Outcomes

Based on the results of our initial scoping review and subsequent stake holder workshops we will include outcomes that assess five domains: 1) Disability; 2) Physical function capacity; 3) Pain on loading/activity; 4) Pain over a specified time; and 5) Pain without further specification. Definitions for each domain and example tools are presented in appendix II.

Types of studies

We will include randomized controlled trials and non-randomized controlled trials.

Context

The context will include primary care, secondary care or community locations in any developed nation (defined as the top 62 countries in the Human Development Index at the time of protocol development)²³ for the findings to be relevant to the UK context.

3.0 Exclusion criteria

We will exclude self-described pilot studies and non-intervention studies where the purpose of the research is to investigate the acute effects of exercise on physiological or biomechanical variables such as pain, collagen turnover or mechanical properties of tendons.

4.0 Methods

Search strategy

The search strategy used for this study was part of a larger search conducted to scope the entire tendinopathy and exercise therapy research base. The search comprised three steps; Firstly, a limited search of MEDLINE and CINAHL using initial keywords (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*) was conducted with analysis of the text words in the titles/abstracts and those used to describe articles to develop a full search strategy. Secondly, the full search strategy was adapted to each database and applied systematically to: MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), JBI Evidence Synthesis, PEDRo, and Epistemonikos (a full search strategy for MEDLINE is presented in appendix III). The following trial registries were also searched: ClinicalTrials.gov, ISRCTN Registry, The Research Registry, EU-CTR (European Union Clinical trials Registry), ANZCTR (Australia and New Zealand Clinical trials Registry). Finally, the third step involved conducting a search of cited and citing articles using Scopus and hand-searching a total of 130 systematic reviews that were identified to include information relevant to exercise therapy and tendinopathy. No limit was placed on language, with research studies published in languages other than English translated via Google Translate or via international collaborations of the review team members. Searches were initiated from 1998 as (i) the heavy load eccentric calf-training protocol for Achilles tendinosis by Alfredsson et al ²⁴ was published in 1998 and may be considered seminal work in the field of tendinopathy, and (ii) there has been a proliferation of research on exercise interventions for tendinopathies post 1998.

Study selection

Proquest® Refworks will be used to manage references and remove duplicates, before importing to Covidence (Melbourne, Australia) to facilitate screening. Two levels of screening will be conducted. First all titles/abstracts will be reviewed, independently, by two members of the research team. Conflicts will be resolved by discussion or by input from a third reviewer. Full-text copies of all studies included at title/abstract screening stage will be retrieved and these will also be screened independently by two members of the research team with conflicts resolved in the same way.

Data extraction

Data will be extracted independently by 8 members of the review team (PS/KC/LA/RM/LG/EP/JS/AP) into pre-piloted excel sheets. Data will be independently coded as described in the accompanying codebook Swinton, Shim, Pavlova, Moss, Maclean, Greig, Parkinson, Morrissey, Alexander, Cooper (2021)

(appendix IV). To quantify reliability, 10% of studies will be selected at random and extraction completed in duplicate. Reliability will be quantified using Cohens K statistic ²⁵ for categorical variables and percentage agreement for continuous variables.

Risk of bias assessment

We will use the Cochrane Collaboration's Risk of Bias tool ²⁶ and all five domains: 1) selection bias; 2) performance bias; 3) detection bias; 4) attrition bias; and 5) reporting bias, to assess risk of bias for all included RCTs. For non-random designs, we will use the ROBINS-I tool ²⁷ and all seven domains: 1) bias due to confounding; 2) bias in selection of participants into the study; 3) bias in classification of interventions; 4) bias due to deviations from intended interventions; and 5) bias due to missing data; 6) bias in measurement of outcomes; and 7) bias in selection of the reported. An overall risk of bias judgement will be made for each outcome and time point as either 'low risk', 'some concerns' or 'high risk' of bias. A single assessment will be made by a reviewer from the team with comments saved to justify selection for each signalling question. To quantify reliability, 10% of studies will be selected at random and extraction completed in duplicate.

Statistical analysis

We will fit treatment-level Bayesian models with standardised mean difference (SMD_{pre}) effect sizes calculated by dividing the relevant mean difference by the pre-intervention standard deviation. As standard, non-controlled effect sizes will be calculated by subtracting baseline values from measurements made at subsequent time-points. Where placebo interventions or no treatment arms are included, the mean difference in the comparator will be subtracted from the mean difference in the resistance exercise intervention. Values will then be standardized by dividing by the pooled baseline standard deviation. Where sufficient data is presented for a single measurement tool, non-standardized effect sizes will also be included to facilitate clinical interpretations. To assess the effects of dose variables, meta-regressions will be performed with continuous covariates where appropriate spread of values are obtained, or where values are clustered binary or trinary categorisations will be made. Meta-regressions will only be performed where data from 10 or more trials are available for covariates or 4 or more trials per level for categorical variables.

Where outcomes are assessed at multiple time-points following baseline measurement, all possible SMD_{pre} values will be calculated. Where required, SMD_{pre} values will be reflected by multiplying by -1 to ensure that positive values represent a positive clinical effect and one that favours resistance exercise. Where baseline standard deviation values are not presented these will be estimated using statistical information presented ²⁸ (e.g. confidence intervals, standard errors, t values, P values, F values) or will be imputed through simple linear regression of the log-transformed standard deviations and means from studies included in the same analysis.²⁹ Three-level Bayesian hierarchical models will be conducted to account for covariances in reporting of multiple outcomes per study. Within study variances of SMD_{pre} values require as input correlation between baseline and follow-up measurements. As this value is generally not presented in studies, informative priors centred on a correlation value of 0.5 will be included. Weakly informative Student-t prior and half-t priors with 3 degrees of freedom and scale parameter equal to 2.5 will be used for intercept and variance parameters (25). Inferences from all analyses will be performed on posterior samples generated by Markov Chain Monte Carlo simulations

and through use of credible intervals and calculated probabilities. Analyses will be performed using the R wrapper package brms interfaced with Stan to perform sampling.³⁰

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Appendix I: Definitions use to define resistance treatment and treatment classes.

Treatment Class	Definition	Treatment	Definition
Resistance	Exercise designed primarily to increase strength of muscles by causing them to produce substantive force against an applied resistance which can take several forms including the mass of the body or its segments, isoinertial resistance, elastic resistance, or strength training equipment such as isokinetic devices. In tendinopathy, the stimulus may also be intended to provoke tendon remodelling, reduce pain and improve function.	Concentric Only	Includes movements where force produced overcomes the resistance such that muscle shortening occurs.
		Eccentric Only	Includes movements where force produced is less than the resistance such that controlled muscle lengthening occurs.
		Concentric and eccentric	Includes movements where force produced exceeds the resistance in one phase and is less than the resistance in another such that controlled muscle lengthening and shortening occurs.
		Isokinetic	Uses specialised exercise equipment such that the resistance is adjusted in real-time to ensure joint angular velocity remains constant.
		Isometric	Includes muscular actions against a resistance such that joint angle remains constant.

Appendix II: Outcome domains and example outcomes included in review.

Domain	ICON Definition	Example Tools
Disability	Composite scores of a mix of patient-rated pain & disability due to the pain, usually relating to tendon-specific activities/tasks	VISA scales; DASH; quick DASH; SPADI; Patient-rated tennis-elbow evaluation questionnaire; Constant Murley Score; WORC (Western Ontario Rotator Cuff Index); AOFAS (American Orthopaedic Foot & Ankle Society); Roles and Maudsley score; ASES (American Shoulder & Elbow Surgeons Index; Tegner activity score; Lysholm knee scale; Pain free function questionnaire; Ankle activity score; Subjective elbow Value (SEV); Placzek score; Shoulder disability questionnaire; International Knee Documentation Committee form (IKDC); Penn Shoulder score (university of Pennsylvania shoulder score) (PSS); Brief pain inventory (BPI); UCLA Shoulder Rating Scale; FILLA - functional index of leg and lower limb; Neer Shoulder Score; Nirschl phase rating scale; American Shoulder and Elbow Surgeon's (MASES) questionnaire; Mayo Elbow Performance Score (MEPS); Shoulder rating questionnaire (SRQ)
Pain on loading/activity	Patient reported intensity of pain performing a task that loads the tendon	VAS; NRS; Pain experience scale;
Pain over a specified time	Patient-reported pain intensity over period of time e.g. morning/night/24-hours/1-week	VAS; NRS Painful days in 3 months
Pain without further specification	Patient asked about pain levels without reference to activity or timeframe	VAS; NRS; Borg CR10 Scale; Pain status
Physical function capacity	Quantitative measures of physical tasks (e.g. hops, times walk, single leg squat) includes muscle strength	Counter movement jump; One-leg triple hop; Single-leg decline squat; Muscle strength measured by dynamometry (hand-held, isokinetic); Repetition maximum; Manual muscle testing.

Appendix III: Search strategy

MEDLINE (EBSCoHost)

Search conducted on 27 April, 2020

Search	Query	Records retrieved
#1	MH exercise OR AB exercis* OR MH “isometric contraction” OR MH rehabilitation OR TX eccentric OR TX concentric OR TX “heavy slow resistance” OR TX isokinetic	362,722
#2	MH tendinopathy OR MH “shoulder injuries” OR MH tendons OR MH “tendon injuries” OR TX tendin* OR TX tendon* OR MH bursitis OR AB bursitis OR MH “posterior tibial tendon dysfunction” OR MH “shoulder impingement syndrome” OR AB “greater trochanteric pain syndrome”	96,490
#3	#1 AND #2	4,363
Limited to 1998 to present		

Appendix IV: Extraction codebook

Column	Heading	Description
Study Details	A	Initials Reviewer
	B	Covidence Identifier
	C	Author
	D	Year
	E	Title
	F	Country
	G	Journal
	H	Aims/Purpose
	I	Tendinopathy type
	J	Study Design
	K	Age Mean
	L	Age SD
	M	Baseline Total N
	N	Training Status Description
	O	Training Status Code
	P	Sex
	Q	BMI Mean
	R	BMI SD
	S	Symptom Severity Mean
	T	Symptom Severity SD
	U	Symptom Duration Mean (Months)
	V	Symptom Duration SD (Months)
	W	Population Comments
Outcomes	X	Outcome Category
	Y	Outcome Tool
	Z	Reflection
	AA	Measurement Time (Weeks)
Intervention	AB	Dominant Treatment
	AC	Total Treatment
	AD	Dose Comparison
	AE	Intervention N
	AF	Intervention Total Duration
	AG	Intervention Adherence %
	AH	Intervention Location
	AI	Intervention Volume
	AJ	Intervention Volume Category
	AK	Intervention Volume Comments
	AL	Intervention Intensity
	AM	Intervention Intensity Category

	AN	Intervention Frequency	Number of sessions per week. Where there is progression, average value is to be entered.
	AO	Intervention Frequency Comments	Any additional information relevant.
	AP	Intervention Progression	Multiple themes to be selected as required 1 = No progression; 2 = NR; 3 = Progression volume; 4 = Progression intensity; 5 = Progression frequency; 6 = Progression specificity; 7 = Progression capacity; 8 = Other
	AQ	Intervention Progression Comments	Any additional information relevant.
Data	AR	Intervention Baseline Mean	Baseline mean for exercise therapy
	AS	Intervention Baseline SD	Baseline standard deviation for exercise therapy
	AT	Intervention Measurement Mean	Mean of outcome for exercise therapy at stated time point
	AU	Intervention Measurement SD	Standard deviation of outcome for exercise therapy at stated time point
	AV	Measurement Comments	State if a different value has been entered for means (e.g. median), a different value for standard deviations (e.g. standard error, IQR, percentiles, distance from mean to upper bound). Provide the relevant statistic (width of CI's, width of percentiles). Also state if data has extracted by digitization

* Outcome Specific