Version Control Table

Version	Author	Purpose/Change	Date
V1-0	Kay Cooper	Protocol approved by NIHR & RGU Ethics (SHSREC20/01)	18.01.2020
V1.1	Kay Cooper	Added funding acknowledgement	31.01.2020
V1.2	Kay Cooper	Appending osf protocols for effectiveness reviews to provide detailed statistical analysis plans	20.05.2021
V1.3	Kay Cooper	Amended mixed methods data synthesis methodology in line with PROSPERO record CRD42020164641– updated aims & objectives and data synthesis & integration to reflect convergent segregated and not convergent integrated review	19.11.2021

1. Title

Exercise therapy for the treatment of tendinopathies: A mixed methods evidence synthesis.

2. Summary of research

Background

Tendinopathy is a common condition in athletic and non-athletic populations. Although it can theoretically affect any tendon in the body, it is most commonly reported in the Achilles, patellar, lateral elbow, rotator cuff and hip tendons. Exercise therapy is the core method of managing tendinopathy, as first or second-line intervention, and despite the plethora of literature on exercise for tendinopathy, uncertainties remain. Exercise has been studied on its own and in combination with other interventions including manual therapies, extracorporeal shockwave therapy, laser therapy, taping and splinting, and various types of injection. Exercise is generally classified by contraction mode (eccentric, concentric, isometric, stretch-shortening) or by intensity of load (e.g., heavy slow resistance exercise, heavily loaded eccentric exercise). A significant body of literature exists comparing one exercise type to another exercise type, to another conservative intervention, or to a control (e.g., “wait and see”). There is also literature concerning factors such as dosage, mode of delivery, and the patient experience. Previous systematic reviews have been conducted, but to date there is no evidence synthesis that combines the exercise related research findings across all tendinopathies and identifies commonalities and heterogenic treatment effects, whilst taking into account relevant variables and participant characteristics.

Aim

The aim of this mixed methods evidence synthesis is to examine the evidence base on exercise therapy for tendinopathies in order to make recommendations for clinical practice and future research.

Review Questions

1. What exercise interventions have been reported in the literature and for which tendinopathies?

2. What outcomes have been reported in studies investigating exercise interventions for tendinopathies?

3. Which exercise interventions are most effective across all tendinopathies?

4. Does type/location of tendinopathy or other specific covariates affect which are the most effective exercise therapies?

5. How feasible and acceptable are exercise interventions for tendinopathies?

Methods

We propose a mixed-methods evidence synthesis comprising a scoping review (review questions 1 & 2), followed by two contingent systematic reviews (review questions 3-5). The scoping review will identify important subgroups who have participated in research, and outcome measures that have been reported. On conclusion of the scoping review, we will hold workshops with rehabilitation specialists and people with tendinopathy. Participants will identify any gaps in the proposed contingent syntheses and make suggestions for additional criteria/outcomes/covariates, which the review team will consider prior to registration of the

protocols for the contingent reviews. The contingent reviews will include a quantitative review of effectiveness and a mixed-methods review of feasibility and acceptability of exercise interventions for tendinopathy. All reviews will follow internationally-recognised guidance, will be conducted in accordance with an *a priori registered/* published protocol, and will comply with PRISMA reporting guidelines, including a summary of findings table created using the GRADE approach where indicated (Grading of Recommendations, Assessment, Development and Evaluation). The syntheses will result in: (i) a map of the existing evidence on exercise therapy for the treatment of tendinopathy (scoping review); (ii) identification of gaps in the existing evidence-base where primary research will be required; and (iii) direct implications for clinical practice. We will hold a second stakeholder workshop on conclusion of the contingent reviews. Stakeholders will help us to interpret the review findings from their perspectives, in order to inform the design of outputs for wide dissemination.

Dissemination & Impact

We will use a range of strategies and types of output to disseminate widely, using audience-specific detail, including publishing in academic journals, presenting at conferences, and using a range of media to coincide with publication of each review (e.g., press release, social media, YouTube videos, infographics). Impact from this mixed-methods evidence synthesis will include: (i) informing evidence-based guidelines for clinical practice; (ii) informing commissioners of health services; (iii) adoption of recommendations by clinicians to the benefit of patients and health services, and (iv) adoption of recommendations on remaining gaps in the evidence-base by research funders in order for funding to be appropriately allocated.

Stakeholder Involvement

In addition to the stakeholder workshops described above, rehabilitation specialists and people with tendinopathy will be part of the steering committee and will contribute throughout the life of the project. We consulted with both groups during the development of this proposal.

3. Background and rationale

The problem

Tendinopathy, commonly defined as “tendon degeneration characterised by a combination of pain, swelling, and impaired performance” can theoretically affect any of the 600+ muscle-tendon units in the body [1], however it is most commonly reported in the Achilles, patellar, lateral elbow, rotator cuff, and hip tendons. Exercise is the mainstay of conservative management of the condition and has focussed largely on eccentric strengthening techniques to date [2]. However, other exercise types, including isotonic and heavy slow resistance exercise have also been recommended for some tendinopathies (e.g., patellar [3]). Exercise may be used in isolation or as an adjunct to other interventions, such as extracorporeal shockwave [4] or laser therapy [5], or following regenerative or orthobiologic procedures such as prolotherapy, platelet-rich plasma or stem-cell treatments [6]. Due to the heterogeneity of tendinopathy (anatomical location, duration), the range of people it can affect (age, gender, activity level, other risk factors and comorbidities) and the variation in exercise approaches (type, dosage, setting) a broad and comprehensive evidence synthesis is essential to inform future clinical practice.

Literature review

A search of MEDLINE, AMED and CINAHL using the terms (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*), limited to English language publications in scientific journals from 2009-2019 returned 1485 results, 183 of which were systematic reviews or meta-analyses. There is therefore a large body of evidence that can be synthesised to make recommendations for practice and research. This body of evidence covers a range of tendinopathies such as those affecting the shoulder [e.g.,7] elbow [e.g.,8], wrist and hand [e.g.,9], and hip regions [e.g.,10], and the hamstring [e.g.,11], patellar [e.g.,12] and Achilles [e.g.,13] tendons.

Exercise has been studied individually or as part of a multi-component intervention, where it is often combined with modalities such as manual therapies [e.g.,14], extracorporeal shockwave therapy [e.g.,15], laser therapy [e.g.,16], taping and splinting [e.g.,17] and various types of injection [e.g.,18]. This approach reflects current expert opinion and evidence syntheses, which recommend exercise-based physiotherapy as the first-line management for tendinopathy with the addition of other interventions in recalcitrant cases [1,19].

Exercise interventions can largely be classified by contraction mode as isotonic-eccentric [3], isotonic-concentric [20], isometric [3] stretch-shortening [21] or by intensity of load compared to maximum; e.g., heavy slow resistance or heavily loaded eccentric exercise [22]; or combinations of two or more of these types. However, other types of exercise, including aquatic therapy and whole-body vibration, have also been reported. In intervention studies, the success of exercise therapy is measured against alternative exercise types, or to splinting or bracing, electro/physical modalities (e.g., ultrasound, extracorporeal shockwave, laser, ice), manual therapies (massage, manual therapy), injection therapies (corticosteroid, prolotherapy) or, less commonly, to a control situation (wait and see).

There is currently no consensus on outcome measures for tendinopathy research. Consequently, a range of measures has been reported in the literature. Studies commonly evaluate the effectiveness of exercise therapy on pain (upon activity or over a specified timeframe [23]) and on function, by way of physical performance tests (e.g., standing heel-rise test for Achilles [24]) and patient-reported outcome measures [25]. These outcomes can be generic (e.g., quality of life) or specific to the body part (eig, DASH/Quick DASH for shoulder), with some tendinopathy-specific measures being utilised (e.g., VISA-A for Achilles; WORC for rotator cuff [25]). Other outcome measures include patient satisfaction, global rating of change, physical activity (particularly in lower limb tendinopathies, and work participation or presenteeism [25].

While most of the literature appears to focus on the effectiveness of exercise in relation to another intervention, or to a control, there is a body of literature concerning dosage [e.g., 26], and contextual factors that may influence effectiveness or interventions, such as supervised versus unsupervised exercise [27]. It is therefore clear that a broad evidence synthesis will be possible, and that a diverse range of factors must be accounted for in the design of the synthesis.

Previous systematic reviews have either compared exercise with other intervention types [29], or compared specific exercise modes such as eccentric, isotonic, or heavy slow resistance [e.g., 3]. Dosage has been considered for Achilles', patellar and rotator cuff tendinopathies [26,28,30], and contextual factors such as supervised or unsupervised exercise have been considered in the case of the upper limb [28]. The novel approach for this proposed evidence synthesis project is to combine the exercise related research across all tendinopathies and identify commonalities and heterogenic treatment effects, whilst also taking into account relevant variables and participant characteristics. It is anticipated that this more extensive modelling approach will greatly enhance existing knowledge regarding the

most effective type and content of exercise treatments across multiple tendinopathy outcomes.

To avoid duplication of existing work, in addition to the search reported above which identified some systematic review protocols, we also searched for reviews in-progress using PROSPERO, Epistemonikos, PEDro, and the Cochrane Database of Systematic Reviews (using tendinopathy and exercise as keywords). Although a number of in-progress reviews were identified (73 registered with PROSPERO), none are similar in scope to the evidence synthesis being proposed here. Many are investigating exercise *per se* and not the relative effects of different types and dosages, and several are limited in scope to conducting one comparison or to investigating a limited number of outcomes. The majority are also concerned with one specific tendinopathy. Since the proposed synthesis will encompass all tendinopathies and all exercise interventions, and will consider a number of important exercise, measurement and participant characteristics, it will add to the body of knowledge and complement findings of existing and in-progress syntheses.

3a. Evidence explaining why this research is needed now

This evidence synthesis is required to aid clinical decision-making, to provide key commissioning data, and to identify gaps where future high-quality research is indicated. The Global Burden of Disease 2010 study highlighted that “other musculoskeletal” conditions, including disorders of the synovium and tendon, are common, accounting for 28.3 million years lived with disability, making them one of the world’s top 10 contributors to global disability burden [31]. Tendinopathy is common not only in athletic populations but also in the general population. For example, a study of prevalence and incidence of lower extremity tendinopathy in a Dutch general population reported rates of 11.83 and 10.52 per 1000 person-years, respectively [32]. Tendinopathies can affect children, adolescents, and adults of all ages, and many tendinopathies have a chronic or recurrent course [1]. Costs to the individual, the NHS and economy (due to absenteeism and loss of productivity) are therefore substantial, and identifying effective interventions is a priority.

Around one in five General Practitioner (GP) appointments in the UK are for musculoskeletal conditions, including tendinopathy. By identifying effective interventions across the range of tendinopathies, GP’s and other first-contact practitioners (e.g., physiotherapists), managing the condition can be confident in delivering effective evidence-based practice. With an ageing population, increasing pressure and demands on primary care, the current staffing crisis within the NHS and the recent role development of musculoskeletal physiotherapists as first contact practitioners in General Practice [33], the need for clear guidance for evidence-based practice has never been more important.

This evidence synthesis will provide evidence of the effectiveness of exercise as a single or multi-component and first or second-line intervention for any tendinopathy. We will establish the effectiveness of different types and formats of exercise for tendinopathy *per se* and by anatomical location and other important subgroups such as age, gender, athleticism, chronicity and comorbidity. The synthesis will result in: (i) a map of the existing evidence on exercise therapy for the treatment of tendinopathy; (ii) identification of gaps in the existing evidence-base where primary research will be required; and (iii) direct implications for clinical practice and commissioners of services.

4. Aims and objectives

The aim of this mixed methods evidence synthesis is to examine the evidence base on exercise therapy for tendinopathies in order to make recommendations for clinical practice and future research. The specific review questions to be addressed are:

1. What exercise interventions have been reported in the literature and for which tendinopathies?

2. What outcomes have been reported in studies investigating exercise interventions for tendinopathies?

3. Which exercise interventions are most effective across all tendinopathies?

4. Does type/location of tendinopathy or other specific covariates affect which are the most effective exercise therapies?

5. How feasible and acceptable are exercise interventions for tendinopathies?

Specific feasibility & acceptability questions are:
1: What is the current knowledge about the feasibility of delivering exercise interventions for tendinopathy from the perspective of those delivering and receiving interventions?
Specifically:
a) How feasible is the delivery of exercise therapy for tendinopathy in terms of rates (e.g., of adherence, attendance, fidelity)?
and
b) What are patients' and healthcare professionals' perceptions of the feasibility of exercise therapy for tendinopathy?
2: What is the current knowledge about acceptability of receiving exercise therapy for tendinopathy from the perspective of people with tendinopathy?
Specifically:
a) How acceptable is exercise therapy in terms of tolerability
and
b) What are patients' and healthcare professionals' perceptions of the acceptability of exercise therapy for tendinopathy

5. Research Plan / Methods

I: Health technology being assessed

The health technology being assessed is exercise therapy (any type or format) for the treatment of any tendinopathy. We will therefore assess any type of exercise therapy, including but not limited to: eccentric, concentric, heavy slow resistance, stretching, cardiovascular, whole-body or combinations of two or more of these exercise types. The exercise therapy may be used as a first or second-line intervention for tendinopathy, and may be delivered in isolation or with adjunct therapies, as described above; we will assess all such scenarios. Exercise therapy 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. We will assess exercise therapy in a supervised or unsupervised (self-management) manner; in any setting, using any mode of delivery by any professional or support worker, including self-management. We will compare different exercise types to each other, to other conservative interventions, and to control settings where this is possible.

II: Study design

We propose a mixed-methods evidence synthesis consisting of an initial scoping review (to address review questions 1 & 2) followed by two contingent systematic reviews incorporating the quantitative and qualitative evidence (to address review questions 3-5). This approach, informed by the approach taken by Pollock et al [34] in their mixed methods synthesis on stakeholder involvement in systematic reviews, is appropriate for addressing clearly defined objectives and assimilating evidence according to relevance, rather than grouping by research design alone [35]. The approach has been implemented successfully by the project

team in a recent comprehensive evidence synthesis project on falls prevention in hospital in-patients and is based on first conducting an initial scoping review [36] to provide a systematic map [35] of the literature. Systematic maps can have several purposes; in this study, the map will: (i) describe the nature of the research field; and (ii) inform the conduct of subsequent (contingent) syntheses (Figure 1).

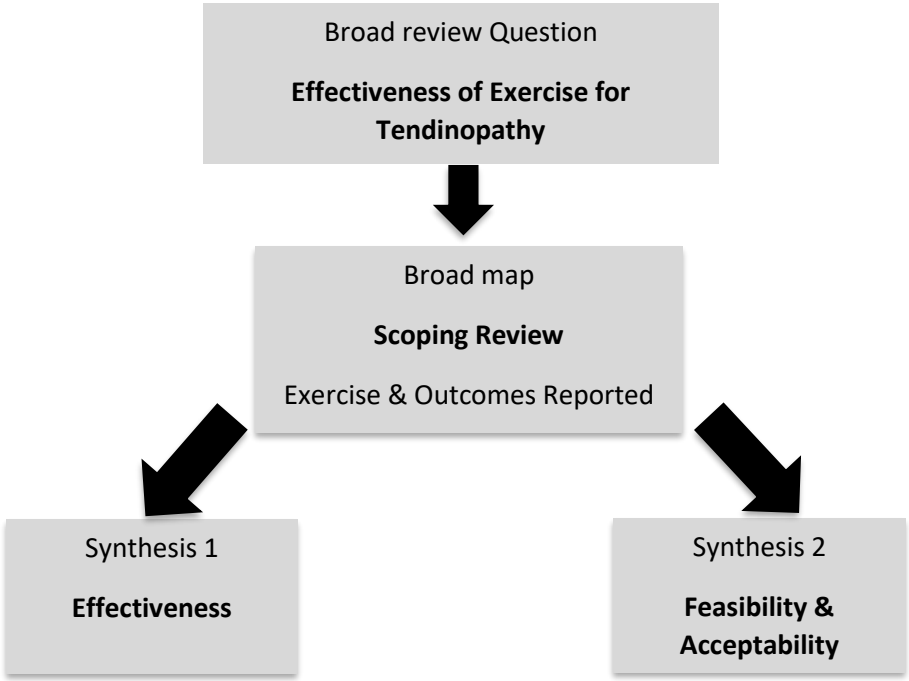

Figure 1: Systematic map leading to several syntheses. Adapted from Gough et al [35]

The scoping review will identify all quantitative and qualitative primary studies on exercise for any tendinopathy, as well as any previous systematic reviews, to ensure that no duplication of previous recent high-quality syntheses are proposed. The proposed contingent reviews include: (i) a synthesis of direct and indirect comparisons of exercise interventions across tendinopathies, which also considers important subgroups and covariates; and (ii) a mixed-methods review, incorporating a range of study designs, including cross-sectional and qualitative, to address the question of feasibility and acceptability. However, the final contingent reviews will be informed by the literature identified by the scoping review (i.e., by what is appropriate and relevant to synthesise) and refined by our stakeholder group.

III: Methods: Scoping review

Scoping reviews are a relatively recent addition to the field of evidence synthesis [36] and have gained popularity in recent years. Arksey & O'Malley's 2005 framework [37], considered by many to be seminal work in the field, prompted further methodological developments with the Joanna Briggs Institute (JBI) producing formal guidance in 2015 [38]. The scoping review conducted for this evidence synthesis project will adhere to these guidelines. The scoping review will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews). [39]. To aid transparency of the methods and facilitate publication of the review, an *a priori* protocol will be fully developed and published on OSF (open science framework www.osf.io) prior to commencing the scoping review, since PROSPERO does not

register scoping review protocols. In addition, it will be submitted to the peer-reviewed journal JBI Evidence Synthesis.

Search strategy

A 3-step search strategy will be developed by the review team. It will incorporate the following. (1): a limited search of MEDLINE and CINAHL using initial keywords (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*) followed by analysis of the text words in the title/abstract and those used to describe articles in order to develop a full search strategy. (2): The full search strategy will be adapted to each database and applied systematically to: MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), JBI Database of Systematic Reviews and Implementation Reports, PEDRo, and Epistemonikos. The following trial registries will also be searched: ClinicalTrials.gov, ISRCTN, The Research Registry, EU-CTR (European Union Clinical trials Registry), ANZCTR (Australia and New Zealand Clinical trials Registry). We will also search for unpublished studies via: Open Grey, MedNar, The New York Academy Grey Literature Report, Ethos, CORE, and Google Scholar. (3): For each article located in steps 1 and 2 we will conduct a search of cited and citing articles using Scopus and hand-searching where necessary. We will not place a language limit on searching; rather, we will include any literature where a translation is accessible via the international collaborations of the project team members. Searching will start from 1998 as:

(i) the heavy load eccentric calf-training protocol for Achilles tendinosis by Alfredsson et al [40] was published in 1998 and may be considered seminal work in the field of tendinopathy;
(ii) there was a proliferation of research on exercise interventions for tendinopathies post-1998; and
(iii) the relevance of including findings from studies conducted more than 20-years ago may be questioned due to advances in research methodologies.

Searching will be undertaken mainly using the EBSCoHost platform via the Robert Gordon University (RGU) library, which facilitates saving searches and exporting to reference management software (Proquest®Refworks). Additional databases will be accessed using the Ovid platform via the NHS Knowledge Network.

The search undertaken during the scoping review will identify literature relevant to the contingent reviews. Each article will be indexed appropriately during the scoping review process to allow relevant studies to be extracted for consideration in each of the contingent reviews. In order for the reviews to be as current and comprehensive as possible, searches will be updated at the start and towards the end of each contingent review. Any additional studies that meet the inclusion criteria will be included.

Inclusion criteria

In keeping with scoping review guidance, a modified PICO (PCoCo) will be used to frame the scoping review [38].

Population: We will include people of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. The term “tendinopathy” has been in widespread use for some time. Some literature may use “tendinitis” or “tendinosis” to describe participants’ tendon pathology as the precise aetiology of tendinopathy remains undetermined [1]. Therefore, we will include all the above terms, as long as the population has a tendon complaint presenting with one or more of pain, swelling and impaired function or performance. Diagnostic criteria vary across tendinopathy studies with there being a need to vary inclusion criteria by tendon site, especially for the shoulder and hip areas where there is a continuum of rotator cuff or gluteal tendinopathy extending through to full tear. Studies that include participants with tendinopathy in the absence of a tear, or a small tear will be

included. Large, full-thickness or massive tears will be excluded, as will groups where the tear size cannot be determined [41].

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; and ultrasound or magnetic resonance imaging confirmation of structural change. Trials 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 [42].

Our definition of tendinopathy therefore includes tendinopathies such as PTTD (posterior tibial tendon dysfunction), tibialis posterior tendinopathy, peroneal tendinopathy, and GTPS (greater trochanteric pain syndrome). However, it excludes plantar heel pain as this condition may respond differently to exercise therapy and could potentially confound the review findings.

Concept: The concept is exercise therapy for the treatment of tendinopathy, therefore the definitions described under "Health technology being assessed" above will be employed.

Context: The context will include primary care, secondary care or community locations in any developed nation (defined as the top 59 countries in the human development index [43], in order for the findings to be relevant to the UK health service.

Types of studies: We will include a broad range of study designs in order to produce a comprehensive map and to inform the contingent reviews. We will include: systematic reviews (to avoid duplicating existing syntheses); quantitative studies including randomised controlled trials and quasi-experimental studies (i.e., studies with a control group; for effectiveness data); mixed-method, descriptive (cross-sectional survey) and qualitative studies (for data on feasibility and acceptability of interventions).

Study selection

Proquest® Refworks will be used to manage references and remove duplicates, before importing to systematic review software (Covidence; Melbourne, Australia) to facilitate screening. Covidence allows members of the review team to conduct screening independently, provides an audit trail of the review process, and allows the creation of bespoke settings (e.g., which members of the study team are eligible to screen and to resolve conflicts). 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 member of the team (experienced 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

The results will be charted to provide a summary of the results that address objectives 1 & 2 (what exercise interventions have been reported; what outcomes have been reported). A draft charting form will be developed at the protocol stage, and may be refined during the review after trialling it on two or three studies to ensure all relevant results can be extracted [38]. The chart will be created using Microsoft Excel® and will include dimensions such as: authors, year of publication, country of origin, study type, purpose, population & sample size, methods, details of exercise therapy and outcome measures used. Details of the exercise therapy will include setting, mode of delivery, type, dosage, and adjunct therapies (if appropriate). Details of the population will include dimensions such as age, gender, body mass index, athleticism, health behaviours (e.g., smoking), co-morbidities (e.g., diabetes) and medication, where reported. The population details will assist in deciding on relevant subgroups to investigate in the contingent reviews. Once the charting form has been piloted

and refined as appropriate, data extraction will be conducted by one reviewer, with independent data extraction by a second reviewer for at least 10% of studies. In keeping with guidance on conducting scoping reviews [38], critical appraisal will not be conducted.

Outcome of scoping review

The results will be presented as a series of figures and tables, i.e., a map of the exercise therapies and outcome measures reported in the literature. The scoping review will itself be disseminated in the form of a journal article, infographic, lay summary (public), and scientific summary (professionals). It will also form the basis for making decisions about the contingent syntheses.

IV: Stakeholder workshop

We will hold stakeholder workshops in Aberdeen and London in month 8 in order to inform interpretation of the review findings and the contingent review stage of the project. Our stakeholders will include: (i) up to 20 rehabilitation specialists (up to 10 in each location) with experience of prescribing exercise therapy for tendinopathy and; (ii) up to 20 people (up to 10 in each location) with experience of receiving exercise therapy for tendinopathy. Tendinopathy affects the athletic and general population and as such, rehabilitation specialists include physiotherapists working in NHS and private settings, and sports and exercise professionals includes coaches, strength and conditioning professionals, personal trainers and fitness professionals. Recruitment of stakeholders will be as follows:

Aberdeen

NHS physiotherapists will be recruited by e-mail invitation via the three lead physiotherapists in the Grampian region of Scotland. Several NHS physiotherapists took part in a stakeholder workshop to inform this proposal and have already expressed an interest in taking part in the proposed workshop. Private physiotherapists will be recruited by e-mailing practices within the same region, as well as snowball sampling via word of mouth from private practices that the authors have pre-established links with. Physiotherapists working with elite athletes will be recruited via the sportscotland institute of sport. Gatekeepers known to the research team will be approached for the recruitment of other rehabilitation specialists (coaches, strength and conditioning professionals, personal trainers and fitness professionals).

People with experience of receiving exercise therapy for tendinopathy will be recruited via: (i) the NHS Grampian Public Involvement Network (e-mail and social media); (ii) RGU social media channels; (iii) using existing networks we will contact local professional and amateur sports clubs and teams such as Sport Aberdeen, RGU:SPORT, Aberdeen Football Club and Aberdeen Amateur Athletics club to request the circulation of information via gatekeepers and; (iv) Elite athletes will be recruited via the sportscotland institute of sport. Several people who have experienced exercise therapy for tendinopathy also took part in a workshop to inform this application. Many have likewise expressed an interest in taking part in the proposed workshop.

London

Rehabilitation specialists will be recruited via relevant gatekeepers in the network of the MSc Sports and Exercise Medicine (SEM) at Queen Mary University (oldest SEM in the world) which includes: leading clinicians working in “Exercise as Medicine” for long-term conditions as well as with elite and recreational athletes and dancers. Specialists will also be recruited from private physiotherapy practices (methods as above) and from Bart’s and the London NHS trust.

People with experience of receiving exercise therapy for tendinopathy will be recruited from an existing PPI network and via the gatekeepers described above.

Prior to each workshop, we will send participants a summary and infographic of the scoping review findings to read. During the workshop, we will present the key findings and our plans for the contingent syntheses. We will invite discussion from participants on their interpretation of the review findings and on the following aspects of the contingent syntheses: inclusion/exclusion criteria; primary and secondary outcomes; subgroups and covariates. This will provide participants with an opportunity to identify any gaps or omissions in the planned syntheses and to make suggestions for additional criteria/outcomes/subgroups/covariates. The research team would consider these suggestions carefully and consult the literature prior to finalising the protocols for the contingent syntheses. The proposed approach is in keeping with guidance from the Cochrane Collaboration on involving stakeholders in systematic reviews [44].

V: Methods - Contingent Review 1: Effectiveness Review

To answer review questions 3 & 4 we will conduct a synthesis of direct and indirect comparisons of exercise interventions across tendinopathies, which also considers important subgroups and covariates. As for the scoping review, an *a priori* protocol will be developed and registered with PROSPERO prior to commencing the review, which will be reported in accordance with PRISMA guidance [45].

Overall approach

To address the extensive research base and overarching questions regarding exercise and tendinopathy, the systematic review will feature comprehensive meta-analyses comprising the most up to date network techniques. The approach adopted will maximise the available information, borrowing strength from individual studies and will provide more complete findings to inform treatment compared with previous reviews and standard pairwise meta-analyses.

Search strategy

Literature will have been located using the search strategy described above (scoping review) and charted in such a way that potentially relevant studies are identified. However, because there will be an 8-month gap between searching and commencing the contingent reviews, the search strategy will be re-run. This will allow identification and inclusion of any studies published in the intervening period.

Inclusion criteria

Population: People of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. Important subgroups and covariates that may explain heterogeneity in relative treatment effects (e.g., symptom severity, chronicity, age, sex, activity levels/training volume, body mass index, co-morbidities, health behaviours and medication use) will be identified *a priori* from the scoping review and incorporated within meta-analyses where appropriate.

Intervention: Exercise therapy for the treatment of tendinopathy, as described above ("Health technology being assessed"). The scoping review will identify exercise therapies that have been reported in the literature including factors such as type, dosage, mode of delivery, whether first or second-line, and whether a single or multi-component intervention. The map produced by the scoping review will allow the research team to identify distinct treatment types to perform network meta-analyses and control for potential confounders such as exercise volume and frequency.

Comparator: We will compare one type of exercise to another, to another conservative intervention (single or combined), or to a control group that received no intervention (e.g., waiting list, wait-and-see). We may compare exercise with surgery; the scoping review will

identify whether there is a body of evidence comparing exercise to surgery that would be relevant to synthesise. If so, then this will be included as an additional comparator.

Outcomes: The scoping review will identify the outcomes that have been reported. However, primary outcomes are likely to include pain and patient-reported function using general or anatomical-location and/or tendinopathy-specific measures, and secondary outcomes may include: quality of life; muscle strength; range of motion; work-related outcomes (e.g., work ability, sick leave); patient satisfaction; return to activities (including sport); and adverse events.

Types of Studies: Randomised controlled trials (RCT) and quasi-experimental studies (with a control group) will be included. We aim to include the best quality research in our analysis. Whilst this will generally be high quality RCTs, where these are not available, (e.g., specific tendinopathies that may not have been subjected to RCT evaluation and/or poor quality RCTs conducted) we will supplement the analysis with lower quality RCTs and quasi-experimental studies, controlling for their inclusion using statistical methods. *This is a pragmatic approach with the aim to include the best available evidence within a review.* We will adhere to the recommendations made in Chapter 24 Cochrane Reviewers' Handbook: Including non-randomized studies on intervention effects; and the nature of this study (i.e., starting with broad scoping review) will allow the review team to identify the available quasi-experimental studies that might be considered for inclusion, prior to finalising the protocol for the effectiveness review. Simulation models will be run based on the likely research base to inform what research and adjustment methods are to be used.

Study selection

Potentially relevant studies will be identified from the scoping review map, and additional studies from the updated search. Studies will be double-screened by title/abstract and full-text for inclusion. Any conflicts will be resolved by a third reviewer (experienced systematic reviewer). The results of the search and screening will be presented in a PRISMA flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram [45].

Assessment of Methodological Quality

Cochrane risk of bias (for RCT) and JBI (for quasi-experimental) tools will be used to assess risk of bias and methodological quality. Critical appraisal will be performed by two independent reviewers and conflicts resolved through discussion or with a third reviewer. Covidence will be used for risk of bias assessment and JBI SUMARI software (Joanna Briggs Institute, Adelaide, Australia) for critical appraisal of quasi-experimental studies. Data will not be excluded based on methodological quality; however, quality will be accounted for in subsequent sensitivity analyses and quantitative downweighting.

Data extraction

Data will be extracted from studies included in the review using a data extraction form designed by the study team. Data extracted will include specific details on the populations, interventions, study methods and outcomes of significance to review questions 3 & 4. Data extraction will be carried out by one reviewer with verification by another reviewer to minimise bias and potential errors. Microsoft Excel® will be used at this stage of the review. Authors of included studies will be contacted in the event of missing information.

Data synthesis

Continuous outcome measures will be used to quantify treatment effects by calculating standardised mean differences. Initially, meta-analyses of direct comparisons will be performed. Model building will then combine both direct and indirect comparisons within a network framework to quantify the probability of each intervention (or combined

interventions) being the most effective (first-best), the second best and so on. All meta-analyses will be performed within a Bayesian random effects framework to facilitate flexible modelling and probabilistic interpretations [46]. Heterogeneity in relative treatment effects will be explored with meta-regression and *a priori* trial-level covariates relating to person and trial characteristics. Associations caused by reporting multiple outcomes due to repeated observations across different follow-up times, and studies incorporating several related variables, will be accounted for by performing multivariate models or including additional hierarchical parameters where appropriate [47]. Model fit, model comparison and network consistency will be assessed using standard methods including residual deviance, deviance information criterion and comparison of direct and indirect evidence, respectively. Sensitivity analyses adjusting for bias based on quality of evidence scores and subsequent down weighting of lower quality evidence will also be included [47]. Models analysed will be conducted with Bayesian Markov chain Monte Carlo methods using the WinBUGS language and the R2WinBUGS package in the R programming environment. Analyses will be performed with non-informative priors and convergence assessed using standard diagnostics.

A network compatible Bayesian selection model will be used to explore the potential impact of publication bias whilst also accounting for consistency assumptions in the network [48]. Any data that cannot be included in the meta-analyses (e.g., due to heterogeneity or missing values) will be included in a narrative synthesis.

While SMDs are readily understandable by people who are comfortable reading meta-analysis reports, it may be that translation to differences on a well-known patient-reported outcome measure in the context of a known MCID (minimal clinically important difference) will be useful. Presentation of results will be guided by our PPI work, and we will consider a range of audience-specific presentation formats for pooled results (both continuous and dichotomous) and tailor these to the relevant audience.

Prior to conducting the network meta-analyses a priori methods regarding data extraction, model building and reporting will be developed and mapped to DECiMAL, NICE and PRISMA guidelines, respectively. These will be documented in the protocol registered on PROSPERO. Furthermore, methods developed to make decisions regarding model building and suitability of data will be informed by calculating model fit and comparison statistics; estimation of “effective sample size” (Thorlund and Mills 2012); and assessing evidence of consistency. Where data are for example removed to resolve issues such as inconsistency, this will be based on a thorough review of the entire evidence base and decisions reported in sufficient depth to facilitate transparency.

Assessing certainty in the findings

A Summary of Findings table will be created using GRADEpro software (McMaster University, Ontario, Canada) and the GRADE approach for grading the quality of evidence. The Summary of Findings table will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias, as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [49].

VI: Methods - Contingent Review 2: Feasibility & Acceptability

Overall approach

The mixed methods review will address review question 5: How feasible and acceptable are exercise interventions for tendinopathy? Mixed methods reviews (also known as mixed methods research syntheses, mixed studies reviews and mixed research syntheses) are a relatively emergent field in evidence synthesis. Mixed methods reviews integrate findings from quantitative and qualitative evidence [50], and are well suited to addressing issues such

as feasibility and acceptability of interventions and patient values and preferences; information which is valuable for the implementation of review findings for example by decision makers and guideline development groups. Mixed methods reviews have proliferated in recent years despite methodological guidance being largely theoretical until recently [51]. The Joanna Briggs Institute published their guidance for mixed methods systematic reviews in 2017 [52]. As the project team includes two JBI certified systematic review trainers and two additional JBI accredited reviewers, and the lead applicant has published two JBI mixed-methods reviews to date, this methodology will be employed for the feasibility and acceptability contingent synthesis. There are different methodological approaches within mixed methods reviews, the choice dependent on the review question. As the questions here can be addressed by quantitative data (1a & 2a) and qualitative data (1b & 2b) respectively, a convergent segregated approach will be taken, where each data type will be synthesised separately, following which the results will be juxtaposed and compared/contrasted [50]. An *a priori* protocol will be developed and registered with PROSPERO prior to commencing the review, which will be reported in keeping with PRISMA guidance [45].

Search strategy

As described above for the effectiveness review, literature will have been located during the scoping review, and an updated search will be undertaken in order to incorporate recent additional studies.

Inclusion criteria

Population: People of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location.

Phenomena of Interest: Feasibility of delivering and acceptability of participating in any exercise therapy for any tendinopathy. In this context, feasibility refers to whether the exercise intervention *"can"* be delivered and will therefore include, but not be limited to, information such as attendance (for formal exercise therapy sessions), intervention fidelity and adherence. Acceptability refers to the acceptability *to patients/clients* of receiving exercise therapy for tendinopathy. As such, it will include, but not be limited to, information such as perceptions, experiences, enjoyment, barriers and facilitators to exercise therapies.

Context: In keeping with the scoping review, the context will include primary care, secondary care or community locations in any developed nation.

Types of studies

Any quantitative, qualitative or mixed methods design that potentially contains data relevant to the review question will be considered for inclusion in the review. It is anticipated that relevant designs will include pilot and/or feasibility studies, cross-sectional studies, and qualitative studies (stand-alone, part of mixed methods studies or embedded in trials). Trials and quasi-experimental studies that include a process evaluation may also be eligible for inclusion. Therefore, studies may be included in both the effectiveness and the feasibility & acceptability review.

Study selection

Potentially relevant studies will be identified from the scoping review map, and additional studies from the updated search. Studies will be double-screened by title/abstract by two independent reviewers. Potentially relevant studies will be retrieved in full, and their citation details imported into JBI SUMARI software. Two independent reviewers will then assess the full text in detail against the inclusion criteria. Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded. Conflicts that arise between reviewers at

each stage will be resolved by discussion, or by consulting a third reviewer. Search and screening results will be presented in a PRISMA flow diagram [45].

Assessment of Methodological Quality

Quantitative studies (and quantitative components of mixed methods studies) will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from JBI SUMARI [https://joannabriggs.org/critical_appraisal_tools]. Likewise, qualitative studies and qualitative components of mixed methods studies will be assessed using the JBI critical appraisal tool for qualitative studies. Disagreements between reviewers will be resolved by discussion or by a third reviewer. The *a priori* mixed methods review protocol will detail whether or not studies are to be excluded based on their methodological quality score; inspecting the scoping review results in terms of the quantity and type of potentially relevant studies will inform this decision.

Data extraction

Data will be extracted from studies included in the review by one reviewer and checked by a second reviewer to minimise errors. A data extraction tool will be developed by the review team. This will be included in the *a priori* protocol. It will be piloted on two or three studies and amended as necessary before being applied across all studies in the review. The data extracted will include specific details about the populations, methods, phenomena of interest, context and outcomes of relevance to the review (i.e., feasibility and acceptability). Quantitative data will be in the form of data-based outcomes of descriptive and/or inferential statistical tests. Qualitative data will be in the form of themes or subthemes with corresponding illustrations (participant quotes or author's interpretations) and will be assigned a level of credibility. Levels of credibility can be Unequivocal (supported by an illustration (e.g., participant quote) that is not open to challenge); Credible (supported by an illustration that may be open to challenge); or Not supported (i.e., findings not supported by data). Any "Not supported" findings will be excluded from the synthesis. Authors of studies will be contacted to request missing or additional data as required.

Data synthesis

Quantitative synthesis
Data will, where possible, be pooled with statistical meta-analysis. Univariate models (e.g., adherence, fidelity, tolerance) will be conducted with proportion data analysed using logit transformation and random effects models used where multiple values are presented from a single study. Where sufficient data is available, sub-analyses or meta-regressions will be used to explore relationships between effect sizes and potential moderator variables including tendinopathy type, exercise type, and assessment duration.
Qualitative synthesis
Qualitative research findings will, where possible be pooled using JBI SUMARI with the meta-aggregation approach. This will involve the aggregation or synthesis of findings to generate a set of statements that represent that aggregation, through assembling the findings and categorizing these findings based on similarity in meaning. These categories are then subjected to a synthesis to produce a comprehensive set of synthesized findings that can be used as a basis for evidence-based practice. Where textual pooling is not possible the findings will be presented in narrative form.

Data integration

The findings of each single method synthesis included in this review will then be configured according to the JBI methodology for mixed methods systematic reviews. This will involve quantitative evidence and qualitative evidence being juxtaposed and organized/linked into a

line of argument to produce an overall configured analysis. Where configuration is not possible the findings will be presented in narrative form.

Due to the complexities associated with integrating quantitative and qualitative findings, it is currently not recommended to assess the certainty of the evidence using the GRADE approach [52]. However, work is ongoing in this area, and the lead applicant is a member of the UK GRADE network steering group. Therefore, should advances be made during the course of the review, they will be implemented accordingly.

Outcome of contingent review 2

The outcome of this stage will be knowledge of the feasibility of delivering exercise therapy for tendinopathy and their acceptability to people with tendinopathy. This knowledge will be crucial for contextualising the findings from the effectiveness review and informing decisions regarding implementation of these findings. It is also highly likely that gaps in the evidence base will be identified by this synthesis, thereby informing future research in this field.

Additional syntheses

At this stage, based on initial literature searching, it is anticipated that the two contingent syntheses detailed above will comprehensively address all five review questions. However, the study design will remain flexible and be dependent on the findings of the scoping review. Therefore, it is possible that inclusion and exclusion criteria may be amended or refined.

VII: Stakeholder Workshop 2

We will hold follow-up stakeholder workshops in Aberdeen and London to help us interpret the results from stakeholders' perspectives, and to inform the design of dissemination materials. We will in the first place invite participants from workshop 1; in the event of any drop-outs we will recruit additional participants as described for workshop 1.

6. Dissemination, Outputs and anticipated impact

Table 1 displays the intended outputs and timescales for delivery. A communication and dissemination strategy will be developed for the start of the project and will be reviewed at each stakeholder meeting; co-applicant Alexander will lead the strategy. We will use a range of output formats and a range of strategies to disseminate as widely as possible to clinicians, academics, decision-makers, and members of the public. The communications departments of RGU, Queen Margaret University London (QMUL), NHS Grampian and sportscotland will assist the research team with press releases promoting the study findings and leading to further promotion on local radio, TV and social media. PPI and rehabilitation specialist steering committee members will facilitate dissemination to relevant groups, and stakeholders who attended workshops 1 & 2 will be invited to assist also.

7. Project timetable

Table 2 details the key stages of the scoping review and 2 contingent syntheses (effectiveness review and feasibility & acceptability review) along with milestones and outputs. Dissemination will continue beyond the end of the funding period. We aim to commence the study on 1st March 2020, and therefore to complete by 31st August 2021.

Table 1: Project outputs

Output	Mechanism	Timescale
Dissemination of findings	Publication of each review in high impact peer reviewed journal, including use of blogs/slides/podcasts as available	Scoping review 2021 Effectiveness review late 2021/early 2022 Feasibility/acceptability review late 2021/early 2022
	Present at Physiotherapy UK (scoping review) & International Scientific Tendinopathy Symposium (Effectiveness and Feasibility/Acceptability reviews)	November 2021 Autumn 2022
	Press release – leading to radio & TV interviews Social media including research team's personal and institutional Twitter accounts (e.g., Co-applicant Morrissey has 5,000 Twitter followers, many of whom are clinicians managing patients with tendinopathy) and @ahp2mintalks YouTube videos Podcasts (e.g., BJSM – attracts up to 10-20,000 listens per podcast) Lay summaries and infographics disseminated via social media and networks that research team and stakeholders are associated with	Coincide with publication of each review
Make recommendations	Engage with professional bodies (e.g., CSP, BASEM) clinical & academic leads (research team's institutions), musculoskeletal lead for Scottish Government AHP Directorate, create bespoke summary for NHS England commissioners Create resource for www.exercise.trekeducation.org	Following publication of final review
Raise awareness	½-day workshop for clinicians (Aberdeen & London) Public launch event (Aberdeen & London) NB These will occur on same day to maximise impact, along with social media promotion Engage with relevant patient groups	Following publication of final review
	Training & Education in best practice	In-service training NHS Grampian, Bart's and the London NHS trust, sportscotland institute of sport

Key: BJSM=British Journal of Sports Medicine; CSP=Chartered Society of Physiotherapy; BASEM=British Association of Sport & Exercise Medicine; AHP=Allied Health Professions

8. Project management

The lead applicant (Cooper) will be responsible for overall management of the project. There will be a lead for each of the three reviews (Scoping: Alexander; Effectiveness: Swinton; Feasibility & acceptability: Cooper). Short weekly meetings of the team members actively conducting the reviews will take place to track progress and address any issues that may arise. Communication between the wider team will take place using Microsoft Teams (GDPR compliant) to enable discussion and document sharing, with the Zoom videoconferencing platform being used to facilitate virtual meetings with co-applicants Brandie and Morrissey. Quarterly Project Management Group meetings will track progress against the project timetable, review tasks conducted to date and plan forthcoming tasks and outputs. Cooper, with support from finance/administration will be responsible for tracking spending, ensuring that the project stays within budget. The research assistant will be line-managed by the lead applicant (Cooper), with support from co-applicant Alexander.

9. Ethics

NHS ethical approval is not required as the project is solely literature-based. Ethical approval is not required for involving patients and the public either (recommendation from NHS Grampian R&D Department); we will follow best practice and recommendations from INVOLVE. We are however seeking approval from the School of Health Sciences Research Ethics Committee for the project in general and specifically for the stakeholder workshops, in order to comply with good research practice.

10. Patient and public involvement

Our PPI strategy has been informed by published guidance from INVOLVE (https://www.invo.org.uk/) and the Cochrane Collaboration, and feedback from PPI participants from previous evidence synthesis projects conducted by the review team. We feel that the following activities represent meaningful PPI:

i) Involving patients and the public to date in developing this application;

ii) Inviting patients and the public to take part in the stakeholder workshop (month 8) to inform the dissemination strategy for the scoping review and the protocols for the contingent syntheses;

iii) Inviting patients and the public to take part in a second stakeholder workshop (month 17) to inform the dissemination and implementation strategy for the project as a whole, and;

iv) Recruiting three people who have experienced exercise therapy for tendinopathy to be active members of our steering committee.

Table 2: Project Timetable

	Scoping	Effectiveness	Feasibility & Acceptability	Stakeholder Workshop	Committee Meeting	Outputs
M1	Finalise protocol Register OSF Submit JBI Evidence Synthesis Detailed search strategy Train RA				PMG Meeting 1	Scoping review protocol OSF & summitted JBI Evidence Synthesis
M2	Searching & selecting studies					
M3	Searching & selecting studies					
M4	Data extraction				PMG Meeting 2	
M5	Data extraction					
M6	Constructing evidence map					Evidence map
M7	Developing outputs				PMG Meeting 3 SSC Meeting 1	
M8	Developing outputs & contingent review protocols			Stakeholder workshop 1: Protocol review		Scoping review manuscript + outputs
M9		Update search Study selection	Update search Study Selection			Contingent review protocols
M10		Critical appraisal	Critical appraisal		PMG Meeting 4	
M11		Critical appraisal Data extraction	Critical appraisal Data extraction			
M12		Data extraction	Data extraction			
M13		Data synthesis	Data synthesis		PMG Meeting 5	
M14		Data synthesis	Data synthesis			
M15		Update search Report writing	Update search Report writing			
M16		Report writing	Report writing		PMG Meeting 6 SSC Meeting 2	
M17		Report writing	Report writing	Stakeholder workshop 2: Dissemination materials & strategy		
M18		Finalise all outputs; Submit manuscripts; Begin dissemination	Finalise all outputs; Submit manuscripts Begin dissemination			Final report + manuscript x 2 + outputs

Key: M=Month; OSF=Open Science Framework; JBI=Joanna Briggs Institute; RA=Research Assistant; PMG=Project Management Group; SSC=Study Steering Committee

11. Success criteria and barriers to proposed work

We will implement the following measures of success:

- Recruitment of three PPI participants and three rehabilitation specialists Project Management Group (month 1)
- Scoping review protocol registration on OSF (prior to start date)
- Scoping review protocol acceptance for publication in JBI Evidence Synthesis (month 4)
- Scoping review completion (month 6)
- Recruitment of up to ten PPI participants and up to ten rehabilitation specialists to each stakeholder workshop (months 8 & 17)
- Scoping review manuscript submitted to peer review journal (month 8)
- Contingent review protocols registered on PROSPERO (month 9)
- Contingent reviews completion (month 16)
- Contingent reviews manuscript submission (month 18)

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Appendix 1: OSF protocols providing detail of statistical analysis plans for contingent synthesis 1 - effectiveness

Empirically derived guidelines for interpreting the effectiveness of exercise therapy for tendinopathies: A protocol.

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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 movement[2] and function[3], 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] In the early phase of rehabilitation, range of movement and flexibility exercises are often initiated and incorporated into strengthening regimes to facilitate improvements in mobility. [12] Included exercises range from static stretches to ballistic actions and variations of contract-relax stretching adapted from the proprioceptive neuromuscular facilitation literature. [12] Effective exercise therapy may also require targeting a range of contributing factors, which not only include muscle weakness and decreased flexibility, but also corticospinal and neuromuscular adaptations resulting from persistent pain. [16] As such, movement retraining or motor control-based exercise interventions have been used to retrain normal patterns of muscle recruitment in the rehabilitation of shoulder-related tendinopathies including impingement, with supportive evidence provided in trials and systematic reviews. [16-19] Similarly, balance and core stabilisation exercises have been recommended for patients presenting with lumbo-pelvic instability in conjunction with patellar and Achilles tendinopathy. [20] Whilst various exercise therapies have been proposed for the treatment of tendinopathy and the overarching aims of reducing pain and disability, and improving function, recommendations are frequently equivocal with no consensus on treatment guidelines for major tendinopathies.

The large range of outcomes reported across research investigating the treatment of tendinopathies has created barriers to the evaluation and synthesis of effectiveness data. Attempts have been made to develop core domains

to facilitate synthesis of outcomes measuring similar constructs. [21] Synthesis has been most effective when conducting meta-analyses, where previous studies have generally quantified effect sizes through calculation of standardised mean differences. The most common approach used to interpret the magnitude of effect sizes and therein the clinical effectiveness of a therapy has been the use of the Cohen's standard benchmarks (small = 0.2, medium = 0.5 and large = 0.8) irrespective of the tendinopathy type, therapy, or population. [22-30] Despite Cohen's [31] recommendations that his general benchmarks should only be used when more relevant context specific information is unavailable, use of these standard benchmarks is ubiquitous throughout behavioural, social and health sciences. However, recent attempts have been made across a range of disciplines to use empirically derived effect size distributions to generate context specific benchmarks. [32-38] Results have generally demonstrated substantive differences between Cohen's benchmarks and those derived empirically, with examples of both under- and over-estimation. In addition, research has shown that even within a single discipline, substantive differences in the distribution of effect sizes can exist across sub-domains. [32] Given the range of tendinopathies and outcome domains commonly investigated, there is potential that the distribution and subsequent appropriate interpretation of therapy effects will be diverse and benefit from the generation of context specific benchmarks. Therefore, the purpose of this study is to perform a large synthesis of the available research investigating exercise therapy for tendinopathies, creating empirically derived thresholds to benchmark interventions and explore potential differences across tendinopathy types and outcome domains.

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 literature [39] 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 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 intervention being assessed is exercise therapy and will comprise five treatment classes: 1) resistance; 2) plyometric; 3) vibration; 4) flexibility and 5) proprioception (see appendix I for definitions). Interventions

combining exercise with other active therapies (e.g. laser, shockwave, manual therapy or injection) will not be included. Exercise therapy 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 exercise intervention to enable appropriate identification of treatment duration, treatment class and exercise dose. In clinical settings it has been recommended that exercise dose is determined by duration, frequency, and intensity; where duration reflects the amount of time accrued in a single exercise session, frequency captures the number of exercise sessions over periods such as a week, and exercise intensity is defined either in absolute terms (such as the metabolic cost of an exercise session), or in relative terms (such as the performance of a given activity as a function of some percentage of measurable maximum capacity. To be included in the review, studies are required to provide sufficient information to describe at least two of the three parameters describing exercise dose. Where sufficient information is not presented in the main text of a study, a search will be made of the publishers' website to check for supplementary files that may include relevant information.

Comparator

Both non-controlled (exercise therapy 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 where at least one intervention arm comprises an exercise therapy that can be categorized according to the treatment classes outlined.

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)[40] 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 [41] 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 and initiate a second deduplication process. 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. Second, 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 extraction codebook (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 [42] for categorical variables and

percentage agreement for continuous variables.

Statistical analysis

To synthesise effects across different measurement outcomes within each domain, standardised mean difference (SMD_{pre}) effect sizes will be calculated by dividing the relevant mean difference by the pre-intervention standard deviation. As standard, non-controlled effect sizes will be calculated for the exercise therapy group 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 exercise therapy. Values will then be standardised by dividing by the pooled baseline standard deviation. Where sufficient data is presented for a single measurement tool, non-standardised effect sizes will also be included to facilitate clinical interpretations. 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. Where baseline standard deviation values are not presented these will be estimated using statistical information presented [43] (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.[44]

The 10th to 90th percentiles will be presented for each effect size distribution in 5-unit increments. In accordance with the most common procedures used in previous studies generating context specific benchmarks, the 25th, 50th and 75th percentile values will be used to identify small, medium, and large effect sizes, respectively.[34,35,38,45] Bayesian three-level hierarchical models with weakly-informative Student-t and half-t priors will be used to model the data and account for covariance of multiple SMD_{pre} values presented in a single study. Normal, skew-normal and t-distribution models will be assessed for fit, and posterior samples used to report 25th, 50th and 75th percentile values with credible intervals. Analyses will be performed using the R wrapper package brms interfaced with Stan to perform Markov chain Monte Carlo sampling.[46]

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Appendix I: Definitions use to define exercise treatment classes.

Treatment Class	**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.
Plyometric	Exercise where a resistance is overcome by a muscle rapidly stretching then shortening
Vibration	Exercise where body segments are held stationary or actively displaced as per definitions for other treatment classes whilst applying a rapid oscillating resistance
Flexibility	Exercise designed to increase joint range of motion and extensibility of muscles and/or associated tissues. Also referred to as range-of-motion exercises or stretching.
Proprioception	Exercise designed to enhance the sensation of the joint relative to body position and movement, sense of force, and to encourage muscular stabilisation of the joint in the absence of external stabilising devices e.g. ankle brace.

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	Identification of individual extracting information
	B	Covidence Identifier	Reference number for Covidence
	C	Author	First author surname *et al.,*
	D	Year	Year of publication
	E	Title	Study title
	F	Country	Country where study was conducted
	G	Journal	Journal name
	H	Aims/Purpose	Study aims/purpose
	I	Tendinopathy type	1=Achilles; 2= Lateral elbow (tennis); 3 = Patellar; 4 = Rotator cuff (SI)
	J	Study Design	RCT = 1; Quasi-experimental = 2
	K	Age Mean	Mean age of study sample as a whole
	L	Age SD	Standard deviation age of study sample as a whole
	M	Baseline Total N	Total sample across all interventions measured at baseline
	N	Training Status Description	Brief description of training status of study sample as a whole
	O	Training Status Code	1 = Performance; 2 = Sporting; 3 = Other
	P	Sex	Percentage female of study sample as a whole
	Q	BMI Mean	Mean BMI of study sample as a whole
	R	BMI SD	Standard deviation of BMI of study sample as a whole
	S	Symptom Severity Mean	Mean severity measure at baseline of study sample as a whole
	T	Symptom Severity SD	Standard deviation of severity measure at baseline of study sample as a whole
	U	Symptom Duration Mean (Months)	Mean symptom duration reported in months
	V	Symptom Duration SD (Months)	Standard deviation symptom duration reported in months
	W	Population Comments	Any additional information relevant to the participants investigated including diagnostic criteria
Outcomes	X	Outcome Category	1 = Disability; 2 = Pain on loading/activity; 3 = Pain over a specified time; 4 = Pain without further specification; 5 = Physical function capacity
	Y	Outcome Tool	Description of outcome tool
	Z	Reflection	1 = Increase in outcome indicates positive treatment; -1 = Decrease in outcome indicates positive treatment
	AA	Measurement Time (Weeks)	Time of measurement in weeks
Intervention	AB	Dominant Treatment Class	**Only one dominant theme to be selected** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Movement pattern retraining
	AC	Total Treatment class	**Multiple themes to be selected as required** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Movement pattern retraining
	AD	Intervention N	Intervention sample size at specified time
	AE	Intervention Total Duration	Total duration of exercise intervention in weeks
	AF	Intervention Adherence %	Reporting of adherence to exercise (reported as a percentage) if applicable
	AG	Intervention Location	Location exercise was performed 1 = Home; 2 = Clinic; 3 = Fitness facility; 4 = NR; 5 = NA
	AH	Intervention Volume	Numerical value describing volume
	AI	Intervention Volume Category	1 = Duration of session (mins); 2 = sets * repetitions; 3 = number of repetitions; 4 = number of sets
	AJ	Intervention Volume Comments	Any additional information relevant.
	AK	Intervention Intensity	Numerical value describing intensity
	AL	Intervention Intensity Category	1 = Absolute; 2 = Relative
	AM	Intervention Frequency	Number of sessions per week. Where there is progression, average value is to be entered.

	AN	Intervention Frequency Comments	Any additional information relevant.
	AO	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
	AP	Intervention Progression Comments	Any additional information relevant.
Control	AQ	Control Comparator	1 = Placebo; 2 = No treatment
	AR	Control Comparator Comments	Any additional information relevant.
Data	AS	Intervention Baseline Mean	Baseline mean for exercise therapy
	AT	Intervention Baseline SD	Baseline standard deviation for exercise therapy
	AU	Intervention Measurement Mean	Mean of outcome for exercise therapy at stated time point
	AV	Intervention Measurement SD	Standard deviation of outcome for exercise therapy at stated time point
	AW	Control Baseline Mean	Baseline mean for control
	AX	Control Baseline SD	Baseline standard deviation for control
	AY	Control Measurement Mean	Mean of outcome for control at stated time point
	AZ	Control Measurement SD	Standard deviation of outcome for control at stated time point
	BA	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 been extracted by digitization

*** Outcome Specific**

Comparison of exercise therapies across multiple tendinopathies: A systematic review and network meta-analysis protocol.

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Conflicts of interest

The authors declare no conflict of interest.

3.0 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 movement[2] and function[3], 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] In the early phase of rehabilitation, range of movement and flexibility exercises are often initiated and incorporated into strengthening regimes to facilitate improvements in mobility. [12] Included exercises range from static stretches to ballistic actions and variations of contract-relax stretching adapted from the proprioceptive neuromuscular facilitation literature. [12] Effective exercise therapy may also require targeting a range of contributing factors, which not only include muscle weakness and decreased flexibility, but also corticospinal and neuromuscular adaptations resulting from persistent pain. [16] As such, movement retraining or motor control-based exercise interventions have been used to retrain normal patterns of muscle recruitment in the rehabilitation of shoulder-related tendinopathies including impingement, with supportive evidence provided in trials and systematic reviews. [16-19] Similarly, balance and core stabilisation exercises have been recommended for patients presenting with lumbo-pelvic instability in conjunction with patellar and Achilles tendinopathy. [20] Whilst various exercise therapies have been proposed for the treatment of tendinopathy and the overarching aims of reducing pain and disability, and improving function, recommendations are frequently equivocal with no consensus on treatment guidelines for major tendinopathies.

Several previous systematic reviews have compared the effectiveness of different exercise therapies, with comparisons investigating exercise specificity (e.g. general vs specific exercises), [21] exercise setting (supervised vs home), [22] contraction mode (e.g. eccentric, concentric or isometric),[23] and application of progressive overload (e.g. progressive vs non-progressive resisted exercise)[24]. While some systematic reviews have provided evidence

of differentiation, [25,26] many have suggested there is equivalence between approaches [21-24] and questioned the validity of entrenched focus on certain exercise protocols.[26] Previous reviews comparing exercise therapies have generally been consistent in their overall approach, with focus on a single tendinopathy, limited range of outcome measures (e.g. pain and function) and restriction to as homogenous an intervention categorisation as possible. As a result, the number of studies included in previous reviews has been limited to between six [21] and fifteen. [23] Additionally, most previous systematic reviews have limited analyses to qualitative syntheses due to concerns regarding both statistical and clinical heterogeneity. However, more recent perspectives in evidence synthesis highlight that with complex interventions statistical heterogeneity should be expected and, as is the case with primary data, variance can present opportunities for informative explanatory analyses. [27] Currently a range of approaches have been developed to best synthesise complex and heterogenous data, with statistical approaches including the use of network meta-analyses (NMA) that potentially combine with meta-regressions. [27] The use of NMA is rapidly increasing in many disciplines with several potential advantages including the ability to combine direct and indirect estimates of treatment effectiveness to enhance precision of estimates.[28] In addition, NMAs may be most effective in areas where there are multiple common treatment options, and an overall hierarchy is unclear. Here NMAs are also particularly suited to assist in creating treatment hierarchies where certain important treatment options are rarely compared directly. When combined with Bayesian methods, therapies can be separated into relatively broad treatment classes or more specific treatments and in both scenarios ranking used to quantify the probability that a specific option is most effective for a given outcome. Where treatments provide similar levels of effectiveness, probability values will be similar, and where there is clear evidence of superiority this should be evident and therefore informative for practitioners. At present there has been limited attempts to conduct NMAs within tendinopathy, with previous studies of conservative treatments primarily limited to Achilles Tendinopathy.[29,30] Comparing 42 treatments and 10 treatment classes across 29 studies, van der Vlist et al.[29] identified strong evidence that all treatment classes were superior to wait-and-see for midportion Achilles tendinopathy, but found no evidence of clinically relevant differences in the effectiveness between active treatments at either 3 or 12-months follow-up. Of the 65 treatments included in the trials, 40 of these comprised exercise therapies and given the associated low costs and few harms, van der Vlist et al.[29] proposed that clinicians should consider at least starting treatment with exercise therapies. The authors identified that the relatively low number of studies included in the review limited the analyses as many of the treatments were not connected to the network and low statistical power negated attempts to explore heterogeneity.[29] Given the extensive use and initial support for exercise therapies across the tendinopathy literature, and the lack of previous attempts to quantitatively synthesise large amounts of effectiveness data across multiple tendinopathy types, the following systematic review and meta-analysis will be conducted. Network structures will be used to compare exercise treatments and treatment classes in attempts to identify a treatment hierarchy. Additionally, the large amount of data synthesised will be used to explore relevant factors that may explain statistical heterogeneity.

4.0 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 literature [31] as well as stakeholder workshops.

Participants

This review will include people of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. 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. Our definition of tendinopathy therefore includes tendinopathies such as PTTD (posterior tibial tendon dysfunction), tibialis posterior tendinopathy, peroneal tendinopathy, and GTPS (greater trochanteric pain syndrome). However, it excludes plantar heel pain as this condition may respond differently to exercise therapy and could potentially confound the review findings.

Intervention

The health technology being assessed is exercise therapy for the treatment of any tendinopathy. Exercise therapies considered for inclusion will comprise five treatment classes: 1) resistance; 2) plyometric; 3) vibration; 4) flexibility and 5) proprioception (see appendix I for definitions). To enable more detailed comparisons, individual treatments will also be defined by sub-categorising resistance, flexibility and proprioception treatment classes (see appendix I). Interventions combining exercise with other active therapies (e.g. laser, shockwave, manual therapy or injection) will not be included. Exercise therapy 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 exercise intervention to enable appropriate identification of treatment duration, treatment class, treatment sub-categorisation and exercise dose. In clinical settings it has been recommended that exercise dose is determined by duration, frequency, and intensity; where duration reflects the amount of time accrued in a single exercise session, frequency captures the number of exercise sessions over periods such as a week, and exercise intensity is defined either in absolute terms (such as the metabolic cost of an exercise session), or in relative terms (such as the performance of a given activity as a function of some percentage of measurable maximum capacity. To be included in the review, studies are required to provide sufficient information to describe at least two of the

three parameters describing exercise dose. Where sufficient information is not presented in the main text of a study, a search will be made of the publishers' website to check for supplementary files that may include relevant information.

Comparator

The review will include studies that compare at least two different exercise treatment classes or at least two different exercise treatments (defined in appendix I) to enable calculation of study pairwise effect sizes.

Outcomes

Based on the results of our initial scoping review and subsequent stake holder workshops we will include outcomes that assess ten domains: 1) Disability; 2) Physical function capacity; 3) Pain on loading/activity; 4) Pain over a specified time; 5) Pain without further specification 6) Patient rating overall condition; 7) Participation; 8) Quality of life; 9) Adverse effects/events; and 10) Range of motion (for studies investigating rotator cuff tendinopathy only). Definitions for each domain and example measurement tools are presented in appendix II.

Types of studies

We will include randomized controlled trials and non-randomized controlled trials where at least two intervention arms include different exercise treatments or treatment classes.

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)[32] 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

The review will be conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating NMAs of health care interventions [33] and the recent GRADE approach to drawing conclusions from NMA using a minimally contextualised framework.[34]

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 [35] 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 (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 [36] for categorical variables and percentage agreement for continuous variables.

Risk of bias assessment

We will use the Cochrane Collaboration's Risk of Bias tool [37] 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 [38] 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 form 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 and class-level Bayesian models. Pairwise effect sizes will be calculated with standardised mean differences (SMD_{pre}) for continuous outcomes and proportional odds models used for binary outcomes. Initially, direct pair-wise comparisons will be estimated. We will then combine direct and indirect comparisons using NMA and hierarchical NMA if possible.[39] Outcomes will be analysed separately according to short (≤12 weeks), medium (13-52 weeks) and long (>52) time frames. Following the GRADE approach for presentation and interpretation of results, we will select a reference intervention defined as the most connected node in the network. To maintain a minimally contextualised framework, we will select a no effect threshold and move any treatment or treatment class above or below the reference if 95% credible intervals do not span the threshold. Second classifications will then be made based on comparisons with treatment or treatment classes moved relative to the reference. In each of the classifications, treatment or treatment classes will be separated into: 1) moderate to high certainty; and 2) low to very low certainty based on risk of bias, inconsistency and indirectness.[40] Inconsistency will be assessed using model-based methods and comparison of residual deviance and the deviance information criterion).[41] Finally, consistency of the treatment and treatment class hierarchies created in previous steps will be assessed by examining pairwise comparisons not previously used. Sources of statistical heterogeneity will only be explored in cases where there are 10 or more trials available per comparison.[29]

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Appendix I: Definitions use to define exercise therapy classes and treatments.

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.
Flexibility	Exercise designed to increase joint range of motion and extensibility of muscles and/or associated tissues. Also referred to as range-of-motion exercises or stretching.	Static	Joint range of motion actions where the movement is held at or near the end range of motion.
		Dynamic	Joint range of motion actions where the movement is performed continuously into and out of the end range of motion.
		PNF	Proprioceptive neuromuscular facilitation is a technique combining passive stretching and isometric action to achieve maximum range of motion.
		Ballistic	Uses the momentum of a moving body or a limb to increase joint range of motion, bouncing into (or out of) a stretched position.

Proprioception	Exercise designed to enhance the sensation of the joint relative to body position and movement, sense of force, and to encourage muscular stabilisation of the joint in the absence of external stabilising devices e.g. ankle brace.	Sense of joint position and force	Exercise aimed at enhancing the ability to perceive joint position and force with minimal external cues.
		Balance	Includes exercise that require the person to keep or return the displacement of centre of gravity over the base of support through various environmental conditions and changes in body position.
		Movement pattern retraining	Exercise aimed at re-education of motor control and movement patterns that may involve specific retraining of under- or over-active muscles and alteration of kinematic rotation +- translation timing between body segments. May also be termed motor control or stabilisation.
Plyometric	Exercise where a resistance is overcome by a muscle rapidly stretching then shortening	Plyometric	Exercise where a resistance is overcome by a muscle rapidly stretching then shortening.
Vibration	Exercise where body segments are held stationary or actively displaced as per definitions for other treatment classes whilst applying a rapid oscillating resistance	Vibration	Exercise where body segments are held stationary or actively displaced as per definitions for other treatment classes whilst applying a rapid oscillating resistance

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.
Patient rating overall condition	Single-assessment numerical evaluation of symptom status	Global impression/rating of change; patient-acceptable symptom status/state
Participation	Patient rating of the level of participation/engagement across areas of their life	Sport participation; return to sport; work ability; return to work; sick leave
Quality of Life	General wellbeing	EQ5D; EQ3D; SF-36 or SF-12; Assessment of Quality of Life (AQoL); Nottingham Health Profile; Gothenburg QoL Instrument
Adverse effects/events	Unwanted unintended effects of treatments	Adverse event reporting
Range of Motion (Shoulder only)	Active or passive range of motion in specified plane, measured in degrees.	Hand-held goniometer; inclinometer

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	Identification of individual extracting information
	B	Covidence Identifier	Reference number for Covidence
	C	Author	First author surname *et al.,*
	D	Year	Year of publication
	E	Title	Study title
	F	Country	Country where study was conducted
	G	Journal	Journal name
	H	Aims/Purpose	Study aims/purpose
	I	Tendinopathy type	1=Achilles; 2= Lateral elbow (tennis); 3 = Patellar; 4 = Rotator cuff (SI)
	J	Study Design	RCT = 1; Quasi-experimental = 2
	K	Age Mean	Mean age of study sample as a whole
	L	Age SD	Standard deviation age of study sample as a whole
	M	Baseline Total N	Total sample across all interventions measured at baseline
	N	Training Status Description	Brief description of training status of study sample as a whole
	O	Training Status Code	1 = Performance; 2 = Sporting; 3 = Other
	P	Sex	Percentage female of study sample as a whole
	Q	BMI Mean	Mean BMI of study sample as a whole
	R	BMI SD	Standard deviation of BMI of study sample as a whole
	S	Symptom Severity Mean	Mean severity measure at baseline of study sample as a whole
	T	Symptom Severity SD	Standard deviation of severity measure at baseline of study sample as a whole
	U	Symptom Duration Mean (Months)	Mean symptom duration reported in months
	V	Symptom Duration SD (Months)	Standard deviation symptom duration reported in months
	W	Population Comments	Any additional information relevant to the participants investigated including diagnostic criteria
Outcomes	X	Outcome Category	1 = Disability; 2 = Pain on loading/activity; 3 = Pain over a specified time; 4 = Pain without further specification; 5 = Physical function capacity; 6 = Patient rating overall condition; 7) Participation; 8) Quality of life; 9) Adverse effects/events; 10) Range of motion
	Y	Outcome Tool	Description of outcome tool
	Z	Reflection	1 = Increase in outcome indicates positive treatment; -1 = Decrease in outcome indicates positive treatment
	AA	Measurement Time (Weeks)	Time of measurement in weeks
Intervention	AB	Dominant Treatment Class	**Only one dominant theme to be selected** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Proprioception
	AC	Total Treatment class	**Multiple themes to be selected as required** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Proprioception
	AD	Dominant Treatment	**Only one dominant theme to be selected** 1 = Concentric only; 2 = Eccentric only; 3 = Concentric and eccentric; 4 = Isokinetic; 5 = Isometric; 6 = Static; 7 = Dynamic; 8 = PNF; 9 = Ballistic; 10 = Joint position & force; 11 = Balance; 12 = Movement pattern retraining; 13 = Plyometric; 14 = Vibration
	AE	Total Treatment	**Multiple themes to be selected as required** 1 = Concentric only; 2 = Eccentric only; 3 = Concentric and eccentric; 4 = Isokinetic; 5 = Isometric; 6 = Static; 7 = Dynamic; 8 = PNF; 9 = Ballistic; 10 = Joint position & force; 11 = Balance; 12 = Movement pattern retraining; 13 = Plyometric; 14 = Vibration
	AF	Intervention N	Intervention sample size at specified time
	AG	Intervention Total Duration	Total duration of exercise intervention in weeks
	AH	Intervention Adherence %	Reporting of adherence to exercise (reported as a percentage) if applicable
	AI	Intervention Location	Location exercise was performed 1 = Home; 2 = Clinic; 3 = Fitness facility; 4 = NR; 5 = NA

	AJ	Intervention Volume	Numerical value describing volume
	AK	Intervention Volume Category	1 = Duration of session (mins); 2 = sets * repetitions; 3 = number of repetitions; 4 = number of sets
	AL	Intervention Volume Comments	Any additional information relevant.
	AM	Intervention Intensity	Numerical value describing intensity
	AN	Intervention Intensity Category	1 = Absolute; 2 = Relative
	AO	Intervention Frequency	Number of sessions per week. Where there is progression, average value is to be entered.
	AP	Intervention Frequency Comments	Any additional information relevant.
	AQ	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
	AR	Intervention Progression Comments	Any additional information relevant.
Data	AS	Intervention Baseline Mean	Baseline mean for exercise therapy
	AT	Intervention Baseline SD	Baseline standard deviation for exercise therapy
	AU	Intervention Measurement Mean	Mean of outcome for exercise therapy at stated time point
	AV	Intervention Measurement SD	Standard deviation of outcome for exercise therapy at stated time point
	AW	Control Baseline Mean	Baseline mean for control
	AX	Control Baseline SD	Baseline standard deviation for control
	AY	Control Measurement Mean	Mean of outcome for control at stated time point
	AZ	Control Measurement SD	Standard deviation of outcome for control at stated time point
	BA	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**

Which treatments are most effective for common tendinopathies? A systematic review and network meta-analysis protocol.

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Conflicts of interest

The authors declare no conflict of interest.

5.0 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 movement[2] and function[3], 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.

The clinical management of symptomatic tendinopathy requires complex clinical reasoning with reference to the pathoanatomical diagnosis. Rehabilitation strategies can vary substantively depending on the site, stage of the tendinopathy, functional baseline, contributing issues within the kinetic chain, and patient factors including activity level, comorbidities, and coexisting presentations.[12] Current research supports the role of appropriate loading in strength training as the primary treatment of tendinopathy.[13] Different principles of loading such as eccentric loading, combined loading, and heavy, slow resistance training (HSRT) have each been recommended with similar goals to initiate tendon adaptations and restore function. However, observable structural change does not always correlate with positive therapeutic outcomes. Most tendinopathies have associated movement dysfunction which may require movement retraining or motor control-based exercises to retrain normal patterns of muscle recruitment. There is also evidence to suggest the role of potential corticospinal involvement or central sensitisation resulting from persistent pain particularly in chronic tendinopathy. Given the complexities involved, treatments may comprise multiple therapy modes with exercise frequently used as an adjunct with ultrasound, extracorporeal shockwave, laser therapy, or following regenerative or ortho-biologic procedures such as prolotherapy, platelet-rich plasma or stem-cell therapies.[14] Additionally, for those with refractory symptoms, surgical interventions may be indicated.

Currently, the best therapy for tendinopathy remains uncertain. Previous systematic reviews have generally focused on single tendinopathies and resorted to qualitative syntheses of evidence due to concerns of both statistical and clinical heterogeneity. Where, meta-analyses have been conducted, these have generally focussed on small numbers of homogenous studies employing conventional pairwise approaches that do not offer comparative effectiveness of the wide range of treatments, leading to a lack of established hierarchy in tendinopathy interventions. More recent perspectives in evidence synthesis highlight that with complex

interventions statistical heterogeneity should be expected and as is the case with primary data, variance presents opportunities for informative explanatory analyses.[15] Currently a range of approaches have been developed to best synthesise complex and heterogenous data, with statistical approaches including the use of network meta-analyses (NMA) that can potentially be combined with meta-regression.[15] Recent NMAs investigating tendinopathy treatments have focused on localised site-specific tendons with pain relief and function as the predominant outcomes.[16-20] Four NMAs have investigated comparative effectiveness of treatments in upper extremity tendinopathies, three of which studied injection therapies in the shoulder [17] or elbow [18,19] while one other focused on non-surgical treatments for chronic calcific tendinitis of the shoulder.[16] In a NMA of non-surgical treatments for patellar tendinopathy of 11 trials, Chen et al. [20] concluded that platelet-rich plasma has the greatest improvements in pain and function compared with other treatment options. However, the review excluded studies that compared different types of exercise therapy from their analysis. Two recent NMAs assessing the effectiveness of evidence-based treatment for adults with Achilles tendinopathy reported somewhat conflicting findings. The review of 29 RCTs by van der Vlist et al. [21] concluded there was strong evidence that all active treatments were superior to wait-and-see, but no one active treatment could be recommended over another. In contrast, Rhim et al. [22] suggested that high-volume injection with corticosteroid and extracorporeal shockwave therapy may be combined with eccentric exercise to produce sustained benefits in Achilles tendinopathy. However, these latter results were based on a small sample size of two pooled studies. All previous NMAs investigating tendinopathy treatments have reported substantive statistical heterogeneity but have not included sufficient data to explore the variance and thereby generate additional relevant clinical findings. Therefore, the purpose of the present systematic review and NMA is to compare the effectiveness of different treatment classes across a range of tendinopathies and outcomes to better establish a treatment hierarchy. Where sufficient data are obtained, the potential for covariates including patient demographics and condition specifics (e.g. symptom severity) to explain statistical heterogeneity will be explored.

6.0 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 literature [14] as well as stakeholder workshops.

Participants

This review will include people of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. 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. Our definition of tendinopathy therefore includes tendinopathies such as PTTD (posterior tibial tendon dysfunction), tibialis posterior tendinopathy, peroneal tendinopathy, and GTPS (greater trochanteric pain syndrome). However, it excludes plantar heel pain as this condition may respond differently to exercise therapy and could potentially confound the review findings.

Intervention

The primary health technology being assessed is exercise therapy for the treatment of any tendinopathy. Exercise therapies considered for inclusion will comprise five treatment classes: 1) resistance; 2) plyometric; 3) vibration; 4) flexibility and 5) movement pattern retraining modalities (see appendix I for definitions). Exercise therapy 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 exercise intervention to enable appropriate identification of treatment class and quantification of exercise dose. In clinical settings it has been recommended that exercise dose is determined by duration, frequency, and intensity; where duration reflects the amount of time accrued in a single exercise session, frequency captures the number of exercise sessions over periods such as a week, and exercise intensity is defined either in absolute terms (such as the metabolic cost of an exercise session), or in relative terms (such as the performance of a given activity as a function of some percentage of measurable maximum capacity. To be included in the review, studies are required to provide sufficient information to describe at least two of the three parameters describing exercise dose. Where sufficient information is not presented in the main text of a study, a search will be made of the publishers' website to check for supplementary files that may include relevant information.

Comparator

The review will include studies that compare exercise therapies with non-active therapies (placebo or no intervention), other conservative therapies or surgery. Definitions of broad and specific treatment classes for the different therapy types are provided in appendix I.

Outcomes

Based on the results of our initial scoping review and subsequent stake holder workshops we will include outcomes that assess ten domains: 1) Disability; 2) Physical function capacity; 3) Pain on loading/activity; 4) Pain over a specified time; 5) Pain without further specification 6) Participant/patient rating overall condition; 7) Participation; 8) Quality of life; 9) Adverse effects/events; and 10) Range of motion (for studies investigating rotator cuff tendinopathy only). Definitions for each domain and example measurement 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

The review will be conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating NMAs of health care interventions [24] and the recent GRADE approach to drawing conclusions from NMA using a minimally contextualised framework.[25]

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 [26] 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 (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 [27] for categorical variables and percentage agreement for continuous variables.

Risk of bias assessment

We will use the Cochrane Collaboration's Risk of Bias tool [28] 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 [29] 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 form 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 class (broad and specific) Bayesian models. Pairwise effect sizes will be calculated with standardised mean differences (SMD_{pre}) for continuous outcomes and proportional odds models used for binary outcomes. Initially, direct pair-wise comparisons will be estimated. We will then combine direct and indirect comparisons using NMA and hierarchical NMA if possible.[30] Outcomes will be analysed separately according to short (≤12 weeks), medium (13-52 weeks) and long (>52) time frames. Following the GRADE approach for presentation and interpretation of results, we will select a reference intervention defined as the most connected node in the network. To maintain a minimally contextualised framework, we will select a no effect threshold and move any treatment or treatment class above or below the reference if 95% credible intervals do not span the threshold. Second classifications will then be made based on comparisons with treatment classes moved relative to the reference. In each of the classifications, treatment classes will be separated into: 1) moderate to high certainty; and 2) low to very low certainty based on risk of bias, inconsistency and indirectness.[31] Inconsistency will be assessed using model-based methods and comparison of residual deviance and the deviance information criterion).[32] Finally, consistency of the treatment and treatment class hierarchies created in previous steps will be

assessed by examining pairwise comparisons not previously used. Sources of statistical heterogeneity will only be explored in cases where there are 10 or more trials available per comparison.[21]

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Appendix I: Definitions use to define broad and specific treatment classes.

Broad Treatment Class	**Definition**	**Specific Treatment Class**	**Definition**
Exercise	Exercise therapy is defined as a regimen or program of physical activities specifically designed and prescribed to correct impairments, restore musculoskeletal function, and/or maintain a state of wellbeing.	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.
		Flexibility	Exercise designed to increase joint range of motion and extensibility of muscles and/or associated tissues. Also referred to as range-of-motion exercises or stretching.
		Proprioception	Exercise designed to enhance the sensation of the joint relative to body position and movement, sense of force, and to encourage muscular stabilisation of the joint in the absence of external stabilising devices e.g. ankle brace.
		Plyometric	Exercise where a resistance is overcome by a muscle rapidly stretching then shortening
		Vibration	Exercise where body segments are held stationary or actively displaced as per definitions for other treatment classes whilst applying a rapid oscillating resistance
Non-active (placebo, sham, wait and see)	Includes any appropriate inactive treatment such as waiting list control, sham shockwave, sham laser, sham taping or true placebo.	Non-active (placebo, sham, wait and see)	Includes any appropriate inactive treatment such as waiting list control, sham shockwave, sham laser, sham taping or true placebo.
Electro-therapy	Modality that delivers therapeutic levels of physical energy into a biologic system e.g. soft tissue.	Shockwave	Extracorporeal shockwave therapy (radial of focussed)
		Laser	Low level laser therapy

		Other	Other less common electro-therapies such as ultrasound, radar and diadynamic current.
Biomechanics	Treatment using external devices that alters the kinematics/kinetics of the limb.	Immobilisation	Any intervention that prevents specific features of joint movement e.g. splinting
		Altered loading	Any intervention aimed at altering tendon loading e.g. taping, tennis elbow clasp/brace and orthotics.
Manual Therapy	Manual therapy is the skilled application of "hands-on" techniques to treat soft tissues and joint structures for the purpose of improving pain, increasing range of motion, stimulating tissue repair response, and/or improving function.	Manual Therapy	Manual therapy is the skilled application of "hands-on" techniques to treat soft tissues and joint structures for the purpose of improving pain, increasing range of motion, stimulating tissue repair response, and/or improving function.
Injection Therapy	Injection therapy for tendinopathy typically involves direct administration of a pharmacologically active drug, or combination of drugs using a syringe and needle or equivalent. It may or may not be image-guided.	Autologous	An autologous injection is an injection of a substance drawn from the patient to whom it is then given, usually at the tendinopathy site after content manipulation with the purpose of stimulating tissue healing.
		Drug	An injection of a classified drug, often mixed with another drug (e.g. corticosteroid with local anaesthetic) for the purpose of reducing pain and stimulating tissue healing.
		Volumetric	An injection deliberately constructed to administer a large volume of fluid to exert a mechanical, as well as pharmacological, effect on the tissues to reduce pain, promote tissue healing and mobilise adherent tissue.
Surgery	Any relevant surgical intervention for tendinopathy	Minimally invasive peritendinous	Minimally invasive procedure with small portals and insertion of surgical tools in the peritendinous area.
		Open intra-tendinous	A more traditional open approach where the tendon is exposed and the peri-tendinous and intra-tendinous areas surgically treated.

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.
Patient rating overall condition	Single-assessment numerical evaluation of symptom status	Global impression/rating of change; patient-acceptable symptom status/state
Participation	Patient rating of the level of participation/engagement across areas of their life	Sport participation; return to sport; work ability; return to work; sick leave
Quality of Life	General wellbeing	EQ5D; EQ3D; SF-36 or SF-12; Assessment of Quality of Life (AQoL); Nottingham Health Profile; Gothenburg QoL Instrument
Adverse effects/events	Unwanted unintended effects of treatments	Adverse event reporting
Range of Motion (Shoulder only)	Active or passive range of motion in specified plane, measured in degrees.	Hand-held goniometer; inclinometer

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	Identification of individual extracting information
	B	Covidence Identifier	Reference number for Covidence
	C	Author	First author surname *et al.,*
	D	Year	Year of publication
	E	Title	Study title
	F	Country	Country where study was conducted
	G	Journal	Journal name
	H	Aims/Purpose	Study aims/purpose
	I	Tendinopathy type	1=Achilles; 2= Lateral elbow (tennis); 3 = Patellar; 4 = Rotator cuff (SI)
	J	Study Design	RCT = 1; Quasi-experimental = 2
	K	Age Mean	Mean age of study sample as a whole
	L	Age SD	Standard deviation age of study sample as a whole
	M	Baseline Total N	Total sample across all interventions measured at baseline
	N	Training Status Description	Brief description of training status of study sample as a whole
	O	Training Status Code	1 = Performance; 2 = Sporting; 3 = Other
	P	Sex	Percentage female of study sample as a whole
	Q	BMI Mean	Mean BMI of study sample as a whole
	R	BMI SD	Standard deviation of BMI of study sample as a whole
	S	Symptom Severity Mean	Mean severity measure at baseline of study sample as a whole
	T	Symptom Severity SD	Standard deviation of severity measure at baseline of study sample as a whole
	U	Symptom Duration Mean (Months)	Mean symptom duration reported in months
	V	Symptom Duration SD (Months)	Standard deviation symptom duration reported in months
	W	Population Comments	Any additional information relevant to the participants investigated including diagnostic criteria
Outcomes	X	Outcome Category	1 = Disability; 2 = Pain on loading/activity; 3 = Pain over a specified time; 4 = Pain without further specification; 5 = Physical function capacity; 6 = Patient rating overall condition; 7) Participation; 8) Quality of life; 9) Adverse effects/events; 10) Range of motion
	Y	Outcome Tool	Description of outcome tool
	Z	Reflection	1 = Increase in outcome indicates positive treatment; -1 = Decrease in outcome indicates positive treatment
	AA	Measurement Time (Weeks)	Time of measurement in weeks
Intervention	AB	Dominant Broad Treatment Class	**Only one dominant theme to be selected** 1 = Exercise; 2 = Non-active; 3 = Electro-therapy; 4 = Biomechanics; 5 = Manual Therapy; 6 = Injection Therapy; 7 = Surgery
	AC	Total Broad Treatment class	**Multiple themes to be selected as required** 1 = Exercise; 2 = Non-active; 3 = Electro-therapy; 4 = Biomechanics; 5 = Manual Therapy; 6 = Injection Therapy; 7 = Surgery
	AD	Dominant Specific Treatment Class	**Only one dominant theme to be selected** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Proprioception; 6 = Non-active; 7 = Shockwave; 8 = Laser; 9 = Electro-therapy Other; 10 = Immobilisation; 11 = Altered loading; 12 = Manual Therapy; 13 = Autolgous; 14 = Drug; 15 = Volumetric; 16 = Minimally invasive; 17 = Open intra-tendinous
	AE	Total Specific Treatment Class	**Multiple themes to be selected as required** 1 = Resistance; 2 = Plyometric; 3 = Vibration; 4 = Flexibility; 5 = Proprioception; 6 = Non-active; 7 = Shockwave; 8 = Laser; 9 = Electro-therapy Other; 10 = Immobilisation; 11 = Altered loading; 12 = Manual Therapy; 13 = Autolgous; 14 = Drug; 15 = Volumetric; 16 = Minimally invasive; 17 = Open intra-tendinous
	AF	Intervention N	Intervention sample size at specified time
	AG	Intervention Total Duration	Total duration of exercise intervention in weeks

	AH	Intervention Adherence %	Reporting of adherence to exercise (reported as a percentage) if applicable
	AI	Intervention Location	Location exercise was performed 1 = Home; 2 = Clinic; 3 = Fitness facility; 4 = NR; 5 = NA
	AJ	Intervention Volume	Numerical value describing volume
	AK	Intervention Volume Category	1 = Duration of session (mins); 2 = sets * repetitions; 3 = number of repetitions; 4 = number of sets
	AL	Intervention Volume Comments	Any additional information relevant.
	AM	Intervention Intensity	Numerical value describing intensity
	AN	Intervention Intensity Category	1 = Absolute; 2 = Relative
	AO	Intervention Frequency	Number of sessions per week. Where there is progression, average value is to be entered.
	AP	Intervention Frequency Comments	Any additional information relevant.
	AQ	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
	AR	Intervention Progression Comments	Any additional information relevant.
Data	AS	Intervention Baseline Mean	Baseline mean for exercise therapy
	AT	Intervention Baseline SD	Baseline standard deviation for exercise therapy
	AU	Intervention Measurement Mean	Mean of outcome for exercise therapy at stated time point
	AV	Intervention Measurement SD	Standard deviation of outcome for exercise therapy at stated time point
	AW	Control Baseline Mean	Baseline mean for control
	AX	Control Baseline SD	Baseline standard deviation for control
	AY	Control Measurement Mean	Mean of outcome for control at stated time point
	AZ	Control Measurement SD	Standard deviation of outcome for control at stated time point
	BA	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**

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

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Conflicts of interest

The authors declare no conflict of interest.

7.0 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 movement[2] and function[3], 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.

8.0 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 literature [22] 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 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

(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 form 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	Identification of individual extracting information
	B	Covidence Identifier	Reference number for Covidence
	C	Author	First author surname *et al.,*
	D	Year	Year of publication
	E	Title	Study title
	F	Country	Country where study was conducted
	G	Journal	Journal name
	H	Aims/Purpose	Study aims/purpose
	I	Tendinopathy type	1=Achilles; 2= Lateral elbow (tennis); 3 = Patellar; 4 = Rotator cuff (SI)
	J	Study Design	RCT = 1; Quasi-experimental = 2
	K	Age Mean	Mean age of study sample as a whole
	L	Age SD	Standard deviation age of study sample as a whole
	M	Baseline Total N	Total sample across all interventions measured at baseline
	N	Training Status Description	Brief description of training status of study sample as a whole
	O	Training Status Code	1 = Performance; 2 = Sporting; 3 = Other
	P	Sex	Percentage female of study sample as a whole
	Q	BMI Mean	Mean BMI of study sample as a whole
	R	BMI SD	Standard deviation of BMI of study sample as a whole
	S	Symptom Severity Mean	Mean severity measure at baseline of study sample as a whole
	T	Symptom Severity SD	Standard deviation of severity measure at baseline of study sample as a whole
	U	Symptom Duration Mean (Months)	Mean symptom duration reported in months
	V	Symptom Duration SD (Months)	Standard deviation symptom duration reported in months
	W	Population Comments	Any additional information relevant to the participants investigated including diagnostic criteria
Outcomes	X	Outcome Category	1 = Disability; 2 = Pain on loading/activity; 3 = Pain over a specified time; 4 = Pain without further specification; 5 = Physical function capacity
	Y	Outcome Tool	Description of outcome tool
	Z	Reflection	1 = Increase in outcome indicates positive treatment; -1 = Decrease in outcome indicates positive treatment
	AA	Measurement Time (Weeks)	Time of measurement in weeks
Intervention	AB	Dominant Treatment	**Only one dominant theme to be selected** 1 = Concentric only; 2 = Eccentric only; 3 = Concentric and eccentric; 4 = Isokinetic; 5 = Isometric
	AC	Total Treatment	**Multiple themes to be selected as required** 1 = Concentric only; 2 = Eccentric only; 3 = Concentric and eccentric; 4 = Isokinetic; 5 = Isometric
	AD	Dose Comparison	1 = Lower dose intervention; 2 = Higher dose intervention
	AE	Intervention N	Intervention sample size at specified time
	AF	Intervention Total Duration	Total duration of exercise intervention in weeks
	AG	Intervention Adherence %	Reporting of adherence to exercise (reported as a percentage) if applicable
	AH	Intervention Location	Location exercise was performed 1 = Home; 2 = Clinic; 3 = Fitness facility; 4 = NR; 5 = NA
	AI	Intervention Volume	Numerical value describing volume
	AJ	Intervention Volume Category	1 = Duration of session (mins); 2 = sets * repetitions; 3 = number of repetitions; 4 = number of sets
	AK	Intervention Volume Comments	Any additional information relevant.
	AL	Intervention Intensity	Numerical value describing intensity
	AM	Intervention Intensity Category	1 = Absolute; 2 = Relative

	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**