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● *Review*

CLASSIFICATION OF TENDON MATRIX CHANGE USING ULTRASOUND IMAGING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract—Ultrasound imaging (US) is an accurate and reliable method used to diagnose tendinopathy. This systematic review was aimed at identifying common criteria and parameters used to diagnose tendinopathy, the methodological quality of studies and the predictive value of US. Nineteen studies met the inclusion criteria, with the Achilles, quadriceps and patella tendons being investigated. Overall, there was significant heterogeneity between the criteria used to diagnose tendinopathy utilising US. The methodological quality of included studies was "good." Additionally, meta-analysis revealed that US-identified abnormalities were predictive of future symptoms, and classification of tendinopathy using three US defined parameters indicated a higher relative risk of developing clinical tendinopathy compared with the use of two US-defined parameters. Further research into the development of a standardised US criterion that incorporates both clinical and US findings is required to allow for greater consistency in the diagnosis of tendinopathy. (E-mail: wesley.matthews@student.bond.edu.au)

Key Words: **Ultrasound imaging, Tendinopathy, Diagnosis, Classification.**

INTRODUCTION

Tendinopathy is an umbrella term for the clinical presentation of tendon pain and dysfunction with accompanying presumed pathologic structural change to the internal tendon matrix (Maffulli et al. 1998; Plinsinga et al. 2015; Rees et al. 2009). It is frequently seen in clinical practice, with the most commonly affected tendons being the Achilles, patellar, rotator cuff and elbow extensors (McCreesh and Lewis 2013; Rees et al. 2009). Overuse tendon injuries account for 30% to 50% of all sports injuries (Scott and Ashe 2006). The catalyst for the onset of tendinopathy can be due to both an increase (Ackermann and Renström 2012; Lewis 2009; Maffulli et al. 1998; Rio et al. 2014; Scott et al. 2015) and a decrease (Arnoczky et al. 2007; Reeves et al. 2005) in mechanical loading of the tendon. It is chronic in nature, with recovery ranging from 3 to 14 mo (Bonde et al. 2003; Khan et al. 2000). Similarly, studies have found that a minimum of 6 mo is required to see significant structural change on imaging (de Vos et al. 2011; Ryan et al. 2010, 2011), although there is some evidence that structural changes can be seen on imaging in a shorter time frame (Docking et al. 2016).

Alternate models have been used to describe the pathogenesis of tendinopathy (Abate et al. 2009; Arnoczky et al. 2007; Cook and Purdam 2009; Fu et al. 2010). Among these models, the continuum model of tendinopathy, as originally proposed by Cook and Purdam, has become a widely accepted theoretical base and method to stage tendinopathy (Cook and Purdam 2009; Cook et al. 2016; McCreesh and Lewis 2013; Rees et al. 2014). The stages identified within this model are distinguished by specific clinical and imaging features (Cook et al. 2016).

There are two primary methods for the diagnosis of tendinopathy (Scott et al. 2013). Clinically, the diagnosis of tendinopathy is centred predominantly on the patient history and clinical examination (Coombes et al. 2015; Lewis 2016; Lewis et al. 2015; Malliaras et al. 2015; Scase et al. 2011; Scott et al. 2013). With respect to specific tests that have been reported to aid the diagnosis of tendinopathy, 2 of 10 commonly used tests (pain on palpation and location of pain) were found to be sufficiently

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reliable and accurate compared with ultrasound imaging (Hutchison et al. 2013). Although pain on palpation has been reported to be sensitive (56%−84%) for reproducing clinical symptoms, it is not specific (47%−73%) in identifying pathologic structural change compared with medical imaging (Cook et al. 2001b; Grimaldi et al. 2017; Hutchison et al. 2013). Furthermore, clinical tests alone do not enable the clinician to determine where their patient may be on the tendinopathy continuum, as stages are primarily based on structural changes (Cook et al. 2016).

Imaging represents a method in which structural changes within the tendon matrix can be identified. Both ultrasound imaging (US) and magnetic resonance imaging (MRI) are used to confirm the presence of structural tendon change in the clinical setting, with the choice of which technique to use based on clinician preference (Scott et al. 2013). Furthermore, for assessment of tendinopathy, US has been reported to have better accuracy (Khan et al. 2003; Warden et al. 2007) and sensitivity (Westacott et al. 2011) compared with MRI. Additionally, US has been reported to have good reliability (Ingwersen et al. 2016) and is considered more patient friendly and cost effective than MRI for the assessment of musculoskeletal conditions, with the ability for dynamic assessment and the measurement of neovascularisation (Lento and Primack 2008; Mapes-Gonnella 2013).

Although numerous studies have examined the sensitivity and accuracy of imaging in identifying tendinopathy (Docking et al. 2015; Scott et al. 2013), research utilising US has been limited to classifying tendon structural change with the use of subjective grading scores established on a multitude of pathologic features (Docking et al. 2015; Ellis and Manuel 2015). In a recent literature review (Ellis and Manuel 2015), the most commonly reported abnormal tendon matrix features, as seen with US, included echogenicity, fusiform swelling, tendon thickness, neovascularisation, fibrillation, calcification and intra-substance tears.

It has been proposed that abnormalities identified on US may be considered a risk factor for the development of future symptoms (Cook et al. 2016; McAuliffe et al. 2016). However, because of the cross-sectional design of many imaging studies (McAuliffe et al. 2016) and the variability in features measured (Ellis and Manuel 2015), uncertainty remains as to the relevance of identified tendon structural abnormalities and their impact on the management of tendinopathy in populations with a high prevalence of tendon-related pain (McAuliffe et al. 2016). Although it is accepted that US-identified tendon abnormalities can be considered a risk factor (Cook et al. 2016; McAuliffe et al. 2016), no study has investigated the predictability of varying classification systems utilising different US-based parameters.

The lack of a homogeneous and standardised US criterion for assessing tendon matrix change makes determining the clinical utility of US in the diagnosis and management of tendinopathy difficult. Identification of commonly used US parameters and classification systems, along with assessment of the predictability of varying parameters, may aid in determining the clinical utility of US and lead to greater homogeneity within this topic area. Thus, the primary aim of this systematic review was to identify the US-based tendinopathy classifications that are reported, including specific tendon matrix features measured. The secondary aim was to appraise the methodological quality of the included studies. The final aim was to utilise meta-analysis to assess the predictive value of the different classification systems identified.

METHODS

Study design

The study followed the methodology proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al. 2009). In line with the PRISMA guidelines, a detailed search strategy was developed and implemented up to August 2017.

Eligibility criteria

Studies were included if they met the following criteria:

- Published full-length research articles in English with the full text available
- Human participants (male or female) of any age, from any athletic or community background
- Longitudinal (randomised or non-randomised) or observational (retrospective or prospective) study design
- Minimum clinical follow-up over 24 h as tendons exhibit an immediate response to load on imaging (Koenig et al. 2010; Rosengarten et al. 2015)
- Tendinopathy in any location
- US as an outcome measure to assess tendon matrix changes (*e.g.,* tendon thickness, echogenicity, collagen organisation, fibrillar pattern, vascularisation)
- Graded or classified tendinopathy stage using either a nominal or ordinal scale.

Studies were excluded if they met the following criteria:

- Patients who had other medical conditions that may affect outcome measures (*e.g.,* Rheumatoid arthritis, diabetes mellitus)
- Cross-sectional studies
- Focus on tendon tear or rupture

- Surgical interventions or injection therapies (corticosteroid or platelet rich plasma) as part of the treatment protocol

Search methods

A detailed, multistep search strategy using PRISMA guidelines was conducted up to August 2017 to identify relevant studies regardless of publication date. The search was conducted in the following databases: Embase, PubMed, SPORTDiscus, EBSCOhost, CINAHL, ProQuest. In addition to the electronic database search, reference lists from included articles were searched for additional articles. To ensure a wider search of relevant articles, key words were truncated to allow for variations in spelling and combined using Boolean operators, as outlined in Table 1. MeSH terms were also used to ensure review of relevant articles. Search strategies for databases were equivalent with the same key words and Boolean operators; however, slight adaptations were made depending on each database's respective characteristics.

Study selection

Search results were imported to EndNote reference management software (EndNote X8.0.1, Clarivate Analytics, Boston, MA, USA). Duplicate records were removed. Titles and abstracts of retrieved articles were screened for eligibility. After the initial screening, the full texts of relevant studies were retrieved for further analysis.

Data extraction

Data extracted included specific details regarding the study design, authors, year of publication, population, intervention methodology, tendon location and length of follow-up. Specific data related to outcome measures included parameters measured and grading or classification system used.

Assessment of methodological quality

The Critical Appraisal Skills Programme (CASP) tool was used to assess the methodological quality of included studies (Critical Appraisal Skills Programme 2017a, 2017b). Studies were assessed using the CASP toolkit independently by two researchers (W.M. and J. F.). The CASP toolkit comprises eight separate checklists to be used depending on study design and enables researchers to critically assess the validity and relevance of published articles. The included articles were assessed for quality using the CASP Cohort Study Checklist (Critical Appraisal Skills Programme 2017a) and the CASP Randomised Controlled Trials Checklist (Critical Appraisal Skills Programme 2017b). The CASP Cohort Study Checklist provides 12 questions to assess study quality. The first 2 questions are screening questions, and the next 10 provide a framework to assess the results of the study, study validity and study relevance. Similarly, the CASP Randomised Controlled Trial Checklist uses 11 questions to assess validity, results and applicability of studies, with the first 2 questions being screening questions.

As was the method of a recent systematic review (McAuliffe et al. 2016), questions 7, 8 and 9 in the CASP Cohort Study Checklist and questions 7 and 8 in the CASP Randomised Controlled Trial Checklist were combined into one question, as they were deemed to investigate similar areas. Most questions are answered with "yes," "no" or "can't tell." The CASP checklists do not provide a scoring system to appraise the quality of evidence. However, although there is a lack of consensus as to what criteria to appraise in quantitative research, it is recognised that quality issues should be highlighted by reviewers (Goldsmith et al. 2007). For the purpose of this systematic review, a scoring system was developed where '1' point was awarded for a "yes" and '0' points for a '"no," with the maximum scores being 12 for the CASP Cohort Study Checklist and 10 for the CASP Randomised Controlled Trial Checklist.

Overall scores were calculated as a percentage, and quality was rated according to the methods reported by Kennelly (2011), where grades were categorized as "poor," "fair" or "good." Studies that scored $\geq$60% were considered as "good" quality, studies that scored between 45% and 59% were "fair" and studies that scored <45% were considered "poor," as has been reported in previous studies (Adhia et al. 2013; Barrett et al. 2014; May et al. 2006, 2010). To ensure consistency of critical appraisal, the criteria used for each question in the CASP checklist was agreed upon between the two reviewers (WM and JF) before commencement of the appraisal process. Inter-rater agreement for each question and overall was calculated using Cohen's Kappa coefficient.

Synthesis and analysis

To determine agreement between raters after the critical appraisal process, Cohen's κ was calculated using the SPSS software package (IBM SPSS Statistics for Macintosh, Version 24.0. IBM, Armonk, NY, USA). Where quantitative methods were appropriate to statistically pool data, a meta-analysis was performed using Review Manager software (Review Manger [RevMan] for Macintosh, Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). A random effects model using the Mantel−Haenszel (M-H) method was used to determine pooled relative risk (RR) of

developing symptomatic tendinopathy with 95% confidence intervals (CIs). Studies were included in the meta-analysis if they used similar methodology, reported on asymptomatic tendons that became symptomatic and provided data on asymptomatic baseline structural changes and development of symptoms at follow-up. Studies were excluded from the meta-analysis if they included symptomatic tendons from baseline, used specific interventions as part of the rehabilitation process or provided insufficient data on baseline or follow-up structural changes. RR was calculated for three subgroups: (1) tendon site (Achilles or patellar); (2) number of parameters used in classifications (3 parameters or 2 parameters); and (3) number of parameters used for specific tendon location.

The heterogeneity between studies was assessed using the I^2 statistic. The I^2 value describes the percentage of variation across the studies that is due to heterogeneity rather than chance, ranging from 0 to 100%, where 0 represents no heterogeneity and increasing values indicate increasing heterogeneity (Higgins et al. 2003). I^2 values of 25% indicate low, 50% moderate and 75% high heterogeneity (Higgins et al. 2003). Similar to a previous systematic review (Smidt et al. 2003), an RR >1.5 was considered clinically significant for the predictability of US-identified abnormalities in asymptomatic tendons becoming symptomatic. RR was summarised using forest plots, and study and publication bias was assessed using funnel plots.

Where meta-analysis was not appropriate because of the heterogeneity of articles and criterion used to assess tendon matrix change on US, a qualitative approach was utilised. Results were synthesised to analyse tendon parameters measured, quality of evidence, predictive value of criteria and relationship to the continuum model of tendinopathy. This data synthesis was then used to inform and guide the development of the proposed criteria, with a greater weighting being placed on articles of "good" quality and parameters that were predictive of tendinopathy.

RESULTS

Search results

The search results are illustrated in the PRISMA flow diagram (Fig. 1). After the removal of duplicates and screening of titles and abstracts against the inclusion criteria, the full texts of 68 articles were retrieved and assessed for inclusion in the systematic review. Of these, 19 articles (Archambault et al. 1998; Boesen et al. 2012; Comin et al. 2013; Cook et al. 2000, 2001a; de Jonge et al. 2010; de Vos et al. 2007; Fredberg and Bolvig 2002; Fredberg et al. 2008; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015) met the inclusion criteria and were included in the systematic review.

Characteristics of included studies

A detailed description of the included studies is provided in Table 2. Of the 19 studies included, 17 were cohort studies (Archambault et al. 1998; Boesen et al. 2012; Comin et al. 2013; Cook et al. 2000, 2001a; de Vos et al. 2007; Fredberg and Bolvig 2002; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015) and 2 were randomised controlled trials (de Jonge et al. 2010; Fredberg et al. 2008). Although no limitations were placed on tendon location, all 19 included studies investigated tendons in the lower limb, with the Achilles, patellar and quadriceps tendons assessed (Archambault et al. 1998; Boesen et al. 2012;

Table 1. Search strategy used for database search

Database	Search strategy
ProQuest	((mesh(tendinopathy) OR all(tendinopath* OR tendonopath* OR tendinitis OR tendinosis)) AND ((mesh(ultrasonography) OR all(ultrasonograph* OR ultrasound OR sonograph*)) AND all(classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)
PubMed	(((("Tendinopathy"[Mesh]) AND (tendinopath* OR tendonopath* OR tendinitis OR tendinosis)) AND "Ultrasonography"[Mesh]) AND (ultrasonograph* OR ultrasound OR sonograph*)) AND (classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)
Embase	('tendinitis'/exp OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND ('echography'/exp OR ultrasonograph* OR ultrasound OR sonograph*) AND classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*
CINAHL	(MH "Tendinopathy+" OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND (MH "Ultrasonography+" OR ultrasonograph* OR ultrasound OR sonograph*) AND classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*
SPORTDiscus	(DE "TENDINITIS" OR DE "ACHILLES tendinitis" OR DE "CALCIFIC tendinitis" OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND (DE "ULTRASONIC imaging" OR DE "DIAGNOSTIC ultrasonic imaging" OR ultrasonograph* OR ultrasound OR sonograph*) AND (classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)

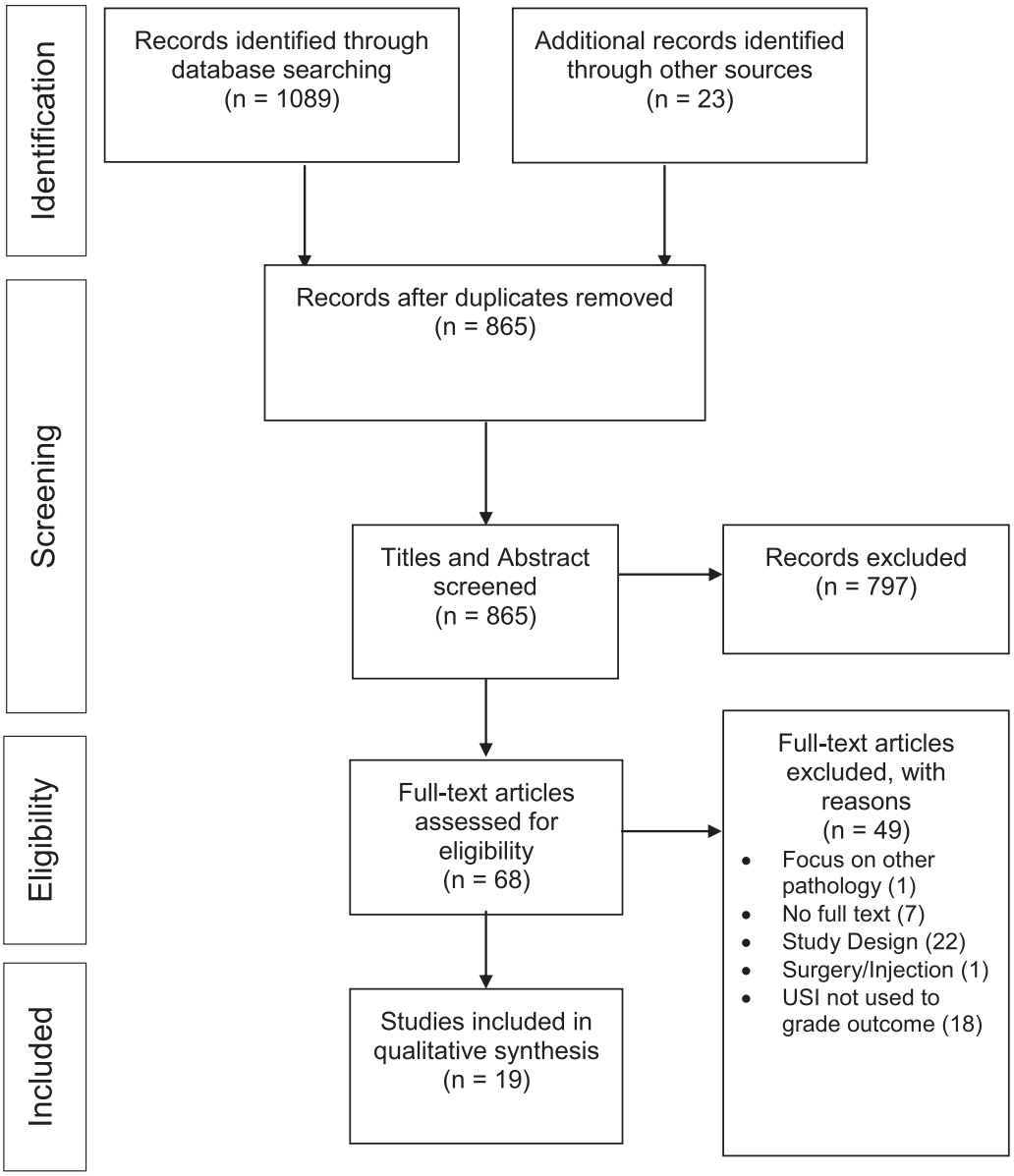

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram. USI = ultrasound imaging.

Comin et al. 2013; Cook et al. 2000, 2001a; de Jonge et al. 2010; de Vos et al. 2007; Fredberg and Bolvig 2002; Fredberg et al. 2008; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 1997, 2003, Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015). Tendon matrix change was classified using either a nominal or an ordinal scale. In a nominal scale, labels are descriptive, allowing for the counting but not ordering of data, whereas an ordinal scale allows for data to be ranked (Stevens 1946).

A nominal grading scale was used in 12 of the included studies (Comin et al. 2013, Cook et al. 2000, 2001a; Fredberg and Bolvig 2002; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 1997; Malliaras et al. 2010; Visnes et al. 2015), and an ordinal scale was used in the remaining 7 studies (Archambault et al. 1998; Boesen et al. 2012; de Jonge et al. 2010; de Vos et al. 2007; Fredberg et al. 2008; Khan et al. 2003; Ooi et al. 2015). The studies that used nominal scales classified tendon structural change as either "normal" or "abnormal" (Comin et al. 2013; Cook et al. 2000, 2001a; Fredberg and Bolvig 2002; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al.

Table 2. Characteristics of included studies

Author	Study design	Demographic characteristics	Population	Tendon	US Structural changes	Classification	US imaging and follow-up
Archambault et al. (1998)	Cohort study	N = 33 (20 M, 13 F) Mean age: 35.8 (18−59)*	Sports medicine clinic	Achilles	Echogenicity Thickness	*1* = Normal (parallel margins, homogeneous) *2* = Enlarged tendon (bowed margins, homogeneous) *3* = Hypo-echoic (with or without enlargement)	US: Initial visit Follow-up: 24.3 mo
Boesen et al. (2012)	Cohort study	N = 86 (56 M, 30 F) Mean age: 21.7 (range N/A)	Badminton	Achilles Patellar Quadriceps	Vascularity	*0* = no Doppler *1* = 1 or 2 tiny foci *2* = <5% colour ROI *3* = 5-24% colour ROI 4 = 25-49% colour ROI *5* = >50% colour ROI	US: Initial and follow-up Follow-up: 8 mo
Comin et al. (2013)	Cohort study	N = 79 (35 M, 44 F) Mean age: 27.6 (18−40)	Ballet dancers	Achilles Patellar	Echogenicity Thickness Vascularity Calcification	*Normal* *Abnormal:* presence of (1) hypo-echogenicity (undefined), or (2) increased thickness (undefined), or (3) vascularity (undefined), or (4) intra-tendon calcification (undefined)	US: Initial visit Follow-up: 24 mo
Cook et al. (2000)	Cohort study	N = 26 (8 M, 18 F) Mean age: N/A (14−18)	Junior basketball	Patellar	Echogenicity Thickness	*Normal* *Abnormal:* presence of (1) hypo-echoic region, or (2) fusiform swelling (all undefined)	US: Initial & follow-up Follow-up: 16 mo (12−24 mo)
Cook et al. (2001a)	Cohort study	N = 24 (24 M) Mean age: 29.8 (at follow-up)	Football Basketball Cricket	Patellar	Echogenicity Thickness	*Normal* *Abnormal:* presence of (1) hypo-echoic region, or (2) fusiform swelling (all undefined)	US: Initial and follow-up Follow-up: 47.1 mo (32−80 mo)
de Jonge et al. (2010)	RCT	N = 50 (63 tendons; 26 M, 37 F) Mean age: 44.6 (26−59)	Sports medicine clinic	Achilles	Vascularity	*0* = no vessels *1* = one vessel mostly in anterior part *2* = one/two vessels throughout tendon *3* = three vessels throughout tendon *4* = >3 large vessels throughout tendon	US: Initial and follow-up Follow-up: 12 mo
de Vos et al. (2007)	Cohort study	N = 52 (63 tendons; 26 M, 37 F) Mean age: 44.6 (26−59)	Sports medicine clinic	Achilles	Vascularity	*0* = no vessels *1+* = one vessel mostly in anterior part *2+* = one/two vessels throughout tendon *3+* = three vessels throughout tendon *4+* = >3 large vessels throughout tendon	US: Initial and follow-up Follow-up: 12 wk

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Table 2 (*Continued*)

Author	Study design	Demographic characteristics	Population	Tendon	US Structural changes	Classification	US imaging and follow-up
Fredberg and Bolvig (2002)	Cohort study	N = 54 (M - 54) Mean age: N/A (18−35)	Soccer	Achilles Patellar	Echogenicity Thickness	*Normal* *Abnormal:* presence of (1) >1-mm thickening (2) >1-mm hypo-echoic region	US: Initial and follow-up Follow-up*:* 12 mo
Fredberg et al. (2008)	RCT	N = 207 (207 M) Mean age: 25.0 (17−37)	Soccer	Achilles Patellar	Echogenicity Thickness	*Normal* *Slightly abnormal:* presence of (1) Thickening 0.5-1 mm (2) Hypo-echoic region 1−2 mm *Severely abnormal:* presence of (1) Thickening >1 mm (2) Hypo-echoic region >2 mm	US: Initial and follow-up Follow-up: 12 mo
Giombini et al. (2013)	Cohort study	N = 37 (15 M, 22 F) Mean age: 27 (16−36)	Fencers	Achilles Patellar Quadriceps	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Focal/diffuse thickening (undefined) (2) Focal/diffuse hypo-echogenicity (undefined) (3) Vascularity >2 (0 = no flow, 1 = flow outside tendon, 2 = 1 or 2 vessels inside tendon, 3 = multiple vessels inside tendon)	US: Initial and follow-up Follow-up: Average 3 y
Gisslén and Alfredson (2005)	Cohort study	N = 60 (29 M, 31 F) Mean age: 17.2 (15−19)	Junior volleyball	Patellar	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Increased thickness (undefined) (2) Hypo-echogenicity (undefined) (3) Vascularity >2 (0 = no flow, 1 = flow outside tendon, 2 = 1 or 2 vessels inside tendon, 3 = multiple vessels inside tendon)	US: Initial and follow-up Follow-up: 7 mo
Gisslén et al. (2007)	Cohort study	N = 22 (11 M, 11 F) Mean age: 16.3 (15−16 at start)	Junior volleyball	Patellar	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Increased thickness (undefined) (2) Hypo-echogenicity (undefined) (3) Vascularity >2 (0 = no flow, 1 = flow outside tendon, 2= 1 or 2 vessels inside tendon, 3 = multiple vessels inside tendon)	US: Initial, regular intervals and follow-up (6 total) Follow-up: 3 y

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Table 2 (*Continued*)

Author	Study design	Demographic characteristics	Population	Tendon	US Structural changes	Classification	US imaging and follow-up
Hirschmüller et al. (2012)	Cohort study	N = 634 (425 M, 209 F) Mean age: 41.2 (17−73)	Long-distance runners	Achilles	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Tendon thickening (undefined) (2) Hypo-/hyper-echogenicity (undefined) (3) Vascularity (0 = no Doppler, 1 = 1 or 2 tiny foci, 2 = <5% colour ROI, 3 = 5%−24% colour ROI, 4 = 25%−49% colour ROI, 5%−50% colour ROI)	US: Initial visit Follow-up: 12 mo
Jhingan et al. (2011)	Cohort study	N = 18 (18 M) Mean age: 23.5 (22−27.5)	Soccer	Achilles	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Thickening (>1 mm) (2) Hypo-echogenicity (>1 mm) (3) Paratendon blurring (4) Vascularity (undefined)	US: Initial visit Follow-up: 12 mo
Khan et al. (1997)	Cohort Study	N = 30 (30 F) Mean age: 24 (range N/A)	Basketball	Patellar	Echogenicity Thickness	*Normal* *Abnormal:* presence of (1) Increased thickness (undefined) (2) Hypo-echogenicity (undefined)	US: Initial and follow-up Follow-up: 18.3 mo (12−34 mo)
Khan et al. (2003)	Cohort study	N = 45 (27 M, 18 F) Mean age - 42 (20−66)	Sports medicine centre	Achilles	Echogenicity Thickness Vascularity	*1* = Normal *2* = Thickened (>6 mm) homogenous echotexture *3* = Hypo-/hyper-echoic areas with/without thickening (>6 mm) Vascularity: normal or abnormal	US: Initial & 12 mo Follow-up: 24 mo
Malliaras et al. (2010)	Cohort study	N = 58 (36 M, 22 F) Mean age: 37.3 (range N/A)	Volleyball	Patellar	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Diffuse thickening (undefined) (2) Hypo-echogenicity (undefined) (3) Vascularity: minimum of 1 vessel >1 mm in length in sagittal plane	US: Initial and monthly Follow-up: 5 mo
Ooi et al. (2015)	Cohort study	N = 41 (25 M, 16 F) Mean age: 37.3 (range N/A)	Runners	Achilles	Echogenicity Thickness Vascularity	*1* = Normal *2* = Heterogeneous echotexture (undefined), bowed tendon margins (undefined), mild	US: Initial (pre-race 1 wk) and 3 d post-race Follow-up: 10 d

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Table 2 (*Continued*)

Author	Study design	Demographic characteristics	Population	Tendon	US Structural changes	Classification	US imaging and follow-up
						neovascularisation (1 or 2 intratendinous vessels >1 mm in length) *3* = Marked thickening (undefined), discrete hypo-echoic areas (undefined), moderate to severe neovascularisation (>2 vessels peripheral and internal)	
Visnes et al. (2015)	Cohort study	N = 158 (74 M, 84 F) Mean age: 16.8 (range N/A)	Junior volleyball	Patellar Quadriceps	Echogenicity Thickness Vascularity	*Normal* *Abnormal:* presence of (1) Hypo-echogenicity (undefined) or (2) Thickness (undefined) (3) Increased vascularity >stage 2 (0 = no flow, 1 = flow outside tendon, 2 = 1 or 2 vessels inside tendon, 3 = multiple vessels inside tendon)	US: Initial and 6-monthly Follow-up: 4 y (average: 1.7 y)

N = number; M = male; F = female; US = ultrasound imaging; N/A = not available, RCT = randomised controlled trial.
*Ranges in parentheses.

1997; Malliaras et al. 2010; Visnes et al. 2015). Three studies that used an ordinal scale graded tendinopathy as grade 1, grade 2, or grade 3 (Archambault et al. 1998; Khan et al. 2003; Ooi et al. 2015), one classified change as "normal," "slightly abnormal" or "severely abnormal" (Fredberg et al. 2008). Two studies used a 5-point scale (de Jonge et al. 2010; de Vos et al. 2007) and one used a 6-point scale (Boesen et al. 2012).

Study scoring and quality

Overall CASP results are summarised in Table 3. Inter-rater agreement was calculated for each question using Cohen's κ. Overall, based on previously published guidelines (Fleiss 1981), Cohen's κ was excellent at 0.93 for the 17 cohort studies and perfect at 1.00 for the 2 randomised controlled trials. Disagreements were discussed, and a consensus was drawn between the two raters. The quality of all studies was rated as "good" according to the categories proposed by Kennelly (2011) and the criteria used in previous studies (Adhia et al. 2013; Barrett et al. 2014; May et al. 2006, 2010).

Synthesis of evidence

A synthesis of evidence is provided in Table 4. Overall, there was significant heterogeneity between the parameters used to assess tendon matrix change and the ability to predict outcomes. Three studies (Boesen et al. 2012; de Jonge et al. 2010; de Vos et al. 2007) measured only one parameter when assessing tendon matrix change, and 6 studies (Archambault et al. 1998; Cook et al. 2000, 2001a; Fredberg and Bolvig 2002; Fredberg et al. 2008; Khan et al. 1997) used two parameters; the remaining 10 studies (Comin et al. 2013; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015) used three parameters. No study included fibrillar pattern as a parameter to assess tendon matrix change. All studies were of good quality according to the previously stated scoring system. Additionally, no criteria were related to the stages of tendinopathy as proposed in the Cook and Purdam (2009) continuum model. There were mixed results when looking at the predictive value of the individual criterion, with 9 studies (Boesen et al. 2012; Comin et al. 2013; Cook et al. 2001a; de Jonge et al. 2010; de Vos et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 2003; Ooi et al. 2015) indicating abnormalities measured on US are unable to predict clinical outcome, and the remaining 10 studies (Archambault et al. 1998; Cook et al. 2000; Fredberg and Bolvig 2002; Fredberg et al. 2008; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Khan et al. 1997; Malliaras et al. 2010; Visnes et al. 2015) indicating US can be a predictor of clinical outcome.

Table 3. Summary of Critical Appraisal Skills Programme scores for included studies

Cohort studies													
Authors	1	2	3	4	5a	5b	6a	6b	7	10	11	12	Score
Archambault et al. (1998)	✓*	✓	✓	✓	✓	✘	✘	✘	✓	✓	✓	✓	75%
Boesen et al. (2012)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Comin et al. (2013)	✓	✓	✘	✓	✘	✘	✓	✓	✓	✓	✓	✓	75%
Cook et al. (2000)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Cook et al. (2001a)	✓	✓	✓	✓	✓	✘	✓	✓	✓	✓	✓	✓	92%
de Vos et al. (2007)	✓	✓	✓	✓	✘	✘	✓	✓	✓	✓	✓	✓	83%
Fredberg and Bolvig (2002)	✓	✓	✓	✓	✘	✘	✓	✓	✓	✓	✓	✓	83%
Giombini et al. (2013)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Gisslén and Alfredson (2005)	✓	✓	✓	✓	✓	✘	✓	✓	✘	✓	✓	✓	83%
Gisslén et al. (2007)	✓	✓	✓	✓	✓	✘	✓	✓	✘	✓	✓	✓	83%
Hirschmüller et al. (2012)	✓	✓	✓	✓	✓	✓	✘	✘	✓	✓	✓	✓	83%
Jhingan et al. (2011)	✓	✓	✘	✓	✘	✘	✓	✓	✓	✓	✓	✓	75%
Khan et al. (1997)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Khan et al. (2003)	✓	✓	✘	✓	✘	✘	✓	✓	✓	✓	✓	✓	75%
Malliaras et al. (2010)	✓	✓	✘	✓	✘	✘	✓	✓	✓	✓	✓	✓	75%
Ooi et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Visnes et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Randomised controlled trials													
Authors	1	2	3	4	5		6		7	9	10	11	
de Jonge et al. (2010)	✓	✓	✓	✘	✓		✓		✓	✓	✓	✓	90%
Fredberg et al. (2008)	✓	✓	✘	✘	✘		✘		✓	✓	✓	✓	60%

*✓ = yes, ✘ = no.

Echogenicity

Echogenicity was the most commonly measured structural change on US, with results summarised in Table 5. Of the included studies, 16 measured echogenicity as a variable for structural change (Archambault et al. 1998; Comin et al. 2013; Cook et al. 2000, 2001a; Fredberg and Bolvig 2002; Fredberg et al. 2008; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015). Overall, abnormal echogenicity was not defined in 13 studies (Archambault et al. 1998; Comin et al. 2013; Cook et al. 2000, 2001a; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Khan et al. 1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015). Two studies (Fredberg and Bolvig 2002; Jhingan et al. 2011) defined abnormal echogenicity as the presence of a hypoechoic region larger than 1 mm, with the remaining study (Fredberg et al. 2008) using different values for the Achilles tendon (0.5 mm) and patellar tendon (1 mm).

Thickness

All studies that measured echogenicity also measured tendon thickness (Archambault et al. 1998; Comin et al. 2013; Cook et al. 2000, 2001a; Fredberg and Bolvig 2002; Fredberg et al. 2008; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al.

Table 4. Synthesis of evidence

Authors	Ultrasound imaging parameter assessed				Study quality	Was the criterion able to predict outcomes?	Is the criterion based on the continuum model?
	Echogenicity	Thickness	Vascularisation	Fibrillar pattern			
Archambault et al. (1998)	✓*	✓	✘	✘	Good	✓	✘
Boesen et al. (2012)	✘	✘	✓	✘	Good	✘	✘
Comin et al. (2013)	✓	✓	✓	✘	Good	✘	✘
Cook et al. (2000)	✓	✓	✘	✘	Good	✓	✘
Cook et al. (2001a)	✓	✓	✘	✘	Good	✘	✘
de Jonge et al. (2010)	✘	✘	✓	✘	Good	✘	✘
de Vos et al. (2007)	✘	✘	✓	✘	Good	✘	✘
Fredberg and Bolvig (2002)	✓	✓	✘	✘	Good	✓	✘
Fredberg et al. (2008)	✓	✓	✘	✘	Good	✓	✘
Giombini et al. (2013)	✓	✓	✓	✘	Good	✓	✘
Gisslén and Alfredson (2005)	✓	✓	✓	✘	Good	✓	✘
Gisslén et al. (2007)	✓	✓	✓	✘	Good	✓	✘
Hirschmüller et al. (2012)	✓	✓	✓	✘	Good	✘	✘
Jhingan et al. (2011)	✓	✓	✓	✘	Good	✘	✘
Khan et al. (1997)	✓	✓	✘	✘	Good	✓	✘
Khan et al. (2003)	✓	✓	✓	✘	Good	✘	✘
Malliaras et al. (2010)	✓	✓	✓	✘	Good	✓	✘
Ooi et al. (2015)	✓	✓	✓	✘	Good	✘	✘
Visnes et al. (2015)	✓	✓	✓	✘	Good	✓	✘

✓ = yes, ✘ = no.

1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015), with results summarized in Table 6. Similarly, 13 studies (Archambault et al. 1998; Comin et al. 2013; Cook et al. 2000, 2001a; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Khan et al. 1997, 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015) determined the presence of increased thickness as "abnormal"; however, cut-off values were not defined. Two studies (Fredberg and Bolvig 2002; Jhingan et al. 2011) used a defined thickness as an increase of 1 mm when related to the normal distal part of the tendon, and 1 study (Fredberg et al. 2008) classified tendon thickening >0.5 mm in the Achilles tendon and thickening >1 mm in the patellar tendon as "abnormal."

Vascularity

Vascularity was measured in 13 of the included studies (Boesen et al. 2012; Comin et al. 2013; de Jonge et al. 2010; de Vos et al. 2007; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Jhingan et al. 2011; Khan et al. 2003; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015). An outline of the criteria used to assess vascularity is provided in Table 7. As outlined in Table 7, 10 studies (Boesen et al. 2012; de Jonge et al. 2010; de Vos et al. 2007; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Hirschmüller et al. 2012; Malliaras et al. 2010; Ooi et al. 2015; Visnes et al. 2015) used varying scales to define "abnormal" vascularity. The remaining 3 studies (Comin et al. 2013; Jhingan et al. 2011; Khan et al. 2003) used the presence of vascularity, with undefined parameters, to determine whether a tendon was classified as "abnormal."

Meta-analysis

Nine of the 19 included studies were eligible for meta-analysis because of similarities in characteristics (Cook et al. 2000, 2001a; Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Jhingan et al. 2011; Khan et al. 1997, 2003; Ooi et al. 2015). The remaining 10 studies could not be included because of insufficient data on the development of symptoms, significant differences in study design and methodology or the inclusion of symptomatic tendons at baseline. Overall, Figure 2 illustrates that tendon abnormalities on US may be predictive of the development of future symptoms in both the patellar and Achilles tendons (RR = 4.78, 95% CI: 2.49−9.15), with low heterogeneity between studies ($I^2 = 0\%$).

Predictive value of parameters

Six studies (Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007; Jhingan et al. 2011; Khan et al. 2003; Ooi et al. 2015) used three parameters (echogenicity, thickness, vascularisation), and 3 studies (Cook et al. 2000, 2001a; Khan et al. 1997) used two parameters (echogenicity and thickness) when assessing structural change in patellar and Achilles tendons on US. Three parameters were found to have an increased risk of developing symptoms (RR = 6.49, 95% CI: 2.49−16.94) compared with

Table 5. Classification of echogenicity

Author	Grading/classification *Nominal scale*	Abnormal echogenicity
Comin et al. (2013)	*Normal* *Abnormal:* Presence of (1) hypo-echogenicity, or (2) increased thickness, or (3) vascularity, or (4) intra-tendon defect (all undefined)	Presence of hypo-echoic regions (undefined)
Cook et al. (2000)	*Normal* *Abnormal:* Presence of (1) hypo-echoic region or (2) fusiform swelling (both undefined)	Presence of hypo-echoic regions (undefined)
Cook et al. (2001a)	*Normal* *Abnormal:* Presence of (1) hypo-echoic region or (2) fusiform swelling (both undefined)	Presence of hypo-echoic regions (undefined)
Fredberg and Bolvig (2002)	*Normal* *Abnormal:* presence of (1) thickening >1 mm or (2) hypo-echoic region >1 mm	Hypo-echoic region >1 mm
Giombini et al. (2013)	*Normal* *Abnormal:* presence of (1) focal/diffuse thickening, or (2) focal/diffuse hypo-echogenicity, or (3) vascularity >grade 2	Focal/diffuse hypo-echogenicity (undefined)
Gisslén and Alfredson (2005)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Presence of hypo-echoic regions (undefined)
Gisslén et al. (2007)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Presence of hypo-echoic regions (undefined)
Hirschmüller et al. (2012)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-/hyper-echogenicity, or (3) vascularity >grade 1	Presence of hyper-/hypo-echoic regions (undefined)
Jhingan et al. (2011)	*Normal* *Abnormal:* presence of (1) thickening >1 mm, or (2) hypo-echogenicity >1 mm, or (3) para-tendon blurring, or (4) vascularity	Hypo-echoic region >1 mm
Khan et al. (1997)	*Normal* *Abnormal:* presence of (1) increased thickness or (2) hypo-echogenicity (both undefined)	Presence of hypo-echoic regions (undefined)
Malliaras et al. (2010)	*Normal* *Abnormal:* presence of (1) diffuse thickening, or (2) hypo-echogenicity (both undefined), or (3) vascularity >1 mm	Presence of hypo-echoic regions (undefined)
Visnes et al. (2015)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Presence of hypo-echoic regions (undefined)
Ordinal scale		
Archambault et al. (1998)	*Grade 1:* Normal (parallel margins, homogeneous) *Grade 2:* Enlarged tendon (bowed margins, homogeneous) *Grade 3*: Hypo-echoic (with or without enlargement)	*Grade 3*: Presence of hypo-echoic regions (undefined)
Fredberg et al. (2008)	*Normal* *Slightly abnormal:* presence of (1) thickening or hypo-echoic region 0.5−1 mm in AT and (2) thickening or hypo-echoic region 1−2 mm in PT *Severely abnormal:* presence of (1) thickening or hypo-echoic region >1 mm AT and (2) thickening or hypo-echoic region >2 mm in PT	Hypo-echoic region >0.5 mm in AT Hypo-echoic region >1 mm in PT
Khan et al. (2003)	*Grade 1:* Normal *Grade 2:* Thickened (>6 mm), homogenous echotexture *Grade 3*: Hyper-/hypo-echoic areas with/without thickening *Vascularity:* normal or abnormal	*Grade 3*: Presence of hyper-/hypo-echoic regions (undefined)
Ooi et al. (2015)	*Grade 1:* Normal *Grade 2:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation *Grade 3:* Discrete hypo-echoic areas, marked thickening, moderate to severe neovascularisation	*Grade 2−3*: Heterogeneous echotexture (undefined) or discrete hypo-echoic regions (undefined)

AT = Achilles tendon, PT = patellar tendon.

Table 6. Classification of tendon thickness

Author	Grading/classification *Nominal scales*	Abnormal thickness
Comin et al. (2013)	*Normal* *Abnormal:* Presence of (1) hypo-echogenicity, or (2) increased thickness, or (3) vascularity, or (4) intratendon defect (all undefined)	Increased thickness (undefined)
Cook et al. (2000)	*Normal* *Abnormal:* Presence of (1) hypo-echoic region or (2) fusiform swelling (both undefined)	Fusiform swelling (undefined)
Cook et al. (2001a)	*Normal* *Abnormal:* Presence of (1) hypo-echoic region or (2) fusiform swelling (both undefined)	Fusiform swelling (undefined)
Fredberg and Bolvig (2002)	*Normal* *Abnormal:* Presence of (1) thickening >1 mm or (2) hypo-echoic region >1 mm	Thickening >1 mm
Giombini et al. (2013)	*Normal* *Abnormal:* Presence of (1) focal/diffuse thickening, or (2) focal/diffuse hypo-echogenicity, or (3) vascularity >grade 2	Focal/diffuse thickening (undefined)
Gisslén and Alfredson (2005)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Increased thickness (undefined)
Gisslén et al. (2007)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Increased thickness (undefined)
Hirschmüller et al. (2012)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-/hyper-echogenicity, or (3) vascularity >grade 1	Increased thickness (undefined)
Jhingan et al. (2011)	*Normal* *Abnormal:* Presence of (1) thickening >1 mm, or (2) hypo-echogenicity >1 mm, or (3) paratendon blurring, or (4) vascularity	Thickening >1 mm
Khan et al. (1997)	*Normal* *Abnormal:* Presence of (1) increased thickness or (2) hypo-echogenicity (both undefined)	Increased thickness (undefined)
Malliaras et al. (2010)	*Normal* *Abnormal:* Presence of (1) diffuse thickening, or (2) hypo-echogenicity (both undefined), or (3) vascularity >1 mm	Increased thickness (undefined)
Visnes et al. (2015)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >grade 2	Increased thickness (undefined)
Ordinal scales		
Archambault et al. (1998)	*Grade 1:* Normal (parallel margins, homogeneous) *Grade 2:* Enlarged tendon (bowed margins, homogeneous) *Grade 3*: Hypo-echoic (with or without enlargement)	*Grade 2–3*: Enlarged tendon with bowed margins (undefined)
Fredberg et al. (2008)	*Normal* *Slightly abnormal:* Presence of (1) thickening or hypo-echoic region 0.5–1 mm in AT and (2) thickening or hypo-echoic region 1–2 mm in PT *Severely abnormal:* Presence of (1) thickening or hypo-echoic region >1 mm AT, and (2) thickening or hypo-echoic region >2 mm in PT	Thickening >0.5 mm in AT Thickening >1 mm in PT
Khan et al. (2003)	*Grade 1:* Normal *Grade 2:* Thickened (>6 mm), homogenous echotexture *Grade 3*: Hyper-/hypo-echoic areas with/without thickening *Vascularity:* normal or abnormal	Tendon diameter >6 mm
Ooi et al. (2015)	*Grade 1:* Normal *Grade 2:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation *Grade 3:* Discrete hypo-echoic areas, marked thickening, moderate to severe neovascularisation	*Grade 2–3*: Increased thickness (undefined)

AT = Achilles tendon; PT = patellar tendon.

Table 7. Classification of vascularity

Author	Grading/classification *Nominal scales*	Abnormal vascularity
Comin et al. (2013)	*Normal* *Abnormal:* presence of (1) hypo-echogenicity, or (2) increased thickness, or (3) vascularity, or (4) intratendon defect (all undefined)	Presence of vascularity (undefined)
Giombini et al. (2013)	*Normal* *Abnormal:* presence of (1) focal/diffuse thickening, or (2) focal/diffuse hypo-echogenicity, or (3) vascularity >2 (0 = no flow, 1= flow outside tendon, 2 = 1 or 2 vessels inside tendon, 3 = multiple vessels inside tendon)	*Grade 2–3*: >1 vessel inside tendon
Gisslén and Alfredson (2005)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >2 (*0* = no flow, *1* = flow outside tendon, *2* = 1 or 2 vessels inside tendon, *3* = multiple vessels inside tendon)	*Grade 2–3*: >1 vessel inside tendon
Gisslén et al. (2007)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >2 (*0*= no flow, *1* = flow outside tendon, *2* = 1 or 2 vessels inside tendon, *3* = multiple vessels inside tendon)	*Grade 2–3*: >1 vessel inside tendon
Hirschmüller et al. (2012)	*Normal* *Abnormal:* Presence of (1) increased thickness, or (2) hypo-/hyper-echogenicity, or (3) vascularity >1 (0 = no Doppler, 1 = 1 or 2 tiny foci, 2 = <5% colour ROI, 3 = 5%–24% colour ROI, 4 = 25%-49% colour ROI, 5 = >50% colour ROI)	*Grade 1–5*: >1 or 2 tiny foci
Jhingan et al. (2011)	*Normal* *Abnormal:* Presence of (1) thickening >1 mm, or (2) hypo-echogenicity >1 mm, or (3) paratendon blurring, or (4) vascularity	Presence of vascularity (undefined)
Malliaras et al. (2010)	*Normal* *Abnormal:* Presence of (1) diffuse thickening, or (2) hypo-echogenicity (both undefined), or (3) vascularity >1 mm	Presence of >1 vessel >1 mm in length
Visnes et al. (2015)	*Normal* *Abnormal:* presence of (1) increased thickness, or (2) hypo-echogenicity, or (3) vascularity >2 (0 = no flow, 1 = flow outside tendon, 2= 1 or 2 vessels inside tendon, 3= multiple vessels inside tendon)	*Grade 2–3*: >1 vessel inside tendon
	Ordinal scales	
Boesen et al. (2012)	*0* = no Doppler *1* = 1 or 2 tiny foci *2* = <5% colour ROI *3* = 5%–24% colour ROI *4* = 25%–49% colour ROI *5* = >50% colour ROI	*Grade 2–5*: > 1 or 2 tiny foci
de Jonge et al. (2010)	*0* = no vessels *1* = 1 vessel mostly in anterior part *2* = 1 or 2 vessels throughout tendon *3* = 3 vessels throughout tendon *4* = >3 large tendons throughout tendon	*Grade 1–4*: > 1 vessel in tendon
de Vos et al. (2007)	*0* = no vessels *1+* = 1 vessel mostly in anterior part *2+* = 1 or 2 vessels throughout tendon *3+* = 3 vessels throughout tendon *4+* = >3 large vessels throughout tendon	*Grade 1–4*: >1 vessel in tendon
Khan et al. (2003)	*Grade 1:* Normal *Grade 2:* Thickened (>6 mm), homogenous echotexture *Grade 3*: Hyper-/hypo-echoic areas with/without thickening *Vascularity:* Normal or abnormal	Presence of vascularity (undefined)
Ooi et al. (2015)	*Grade 1:* Normal *Grade 2:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation (1 or 2 intratendinous vessels >1 mm in length) *Grade 3:* Discrete hypo-echoic areas, marked thickening, moderate to severe neovascularisation (>2 vessels peripheral and internal)	*Grade 2–3*: >1 vessel >1 mm in length

ROI = region of interest.

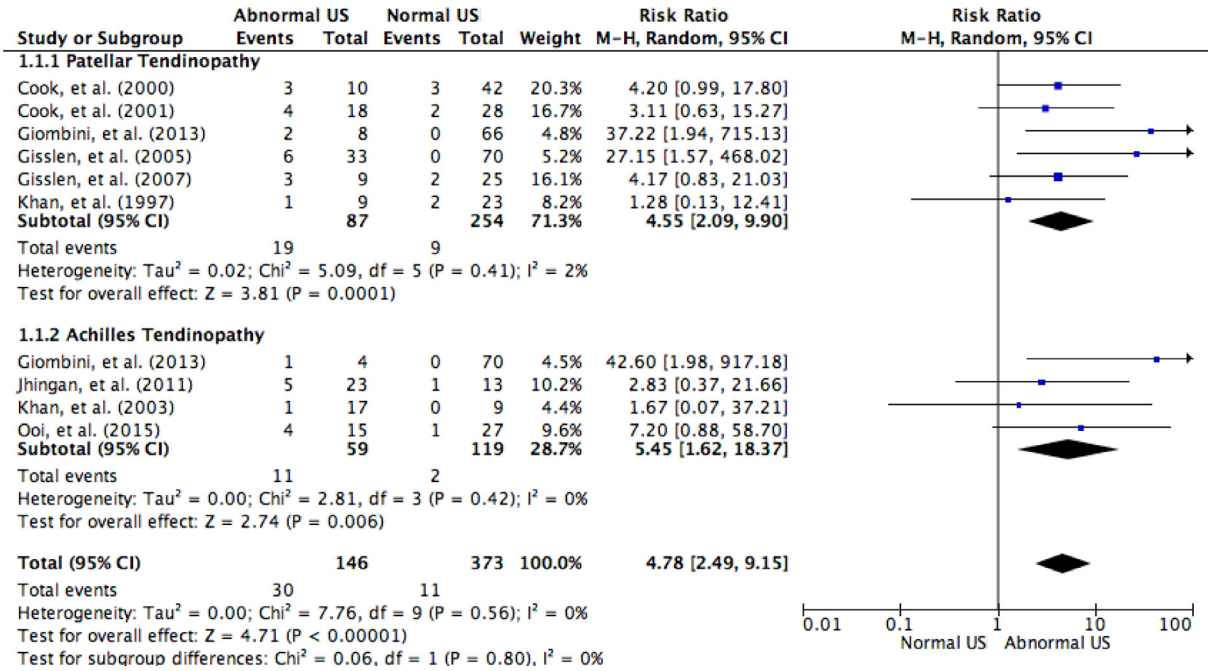

Fig. 2. Meta-analysis results for studies using US to predict symptomatic Achilles and patellar tendinopathy. US = ultrasound imaging; CI = confidence interval; M-H = Mantel–Haenszel.

those studies using two parameters (RR = 3.66, 95% CI: 1.15–11.62). I^2 values indicated low heterogeneity across subgroups (three parameters: $I^2 = 7\%$, two parameters: $I^2 = 6\%$). These data are illustrated in Figure 3.

In the patellar tendon, 3 studies (Giombini et al. 2013; Gisslén and Alfredson 2005; Gisslén et al. 2007) used three parameters to assess structural change, and 3 studies (Cook et al. 2000, 2001a; Khan et al. 1997) assessed change using two parameters. Figure 4 illustrates that three parameters (RR = 10.42, 95% CI: 2.34–46.37) may indicate an increased risk of future symptoms compared with the use of two parameters (RR = 3.03, 95% CI: 1.15–7.97). I^2 analysis revealed low heterogeneity across both subgroups (three parameters: $I^2 = 20\%$, two parameters: $I^2 = 0\%$). All 4 studies assessing the Achilles tendon (Giombini et al. 2013; Jhingan et al. 2011; Khan et al. 2003; Ooi et al. 2015) used three parameters and found an increased risk for developing symptoms (RR = 5.45, 95% CI: 1.62–18.37). Heterogeneity was low between the studies ($I^2 = 0\%$).

Statistical significance was found for the predictive value of US assessment of the tendon matrix for both the Achilles ($p = 0.006$) and patellar ($p = 0.0001$) tendons. There was no statistical difference between the two groups ($p = 0.80$). Similarly, both three parameters ($p = 0.0001$) and two parameters ($p = 0.03$) were determined to be statistically significant for predicting symptom development without a statistical difference between the two groups ($p = 0.45$). In the patellar tendon, there was statistical significance for the predictive value of both three parameters ($p = 0.002$) and two parameters (0.02), with no statistical difference between groups ($p = 0.17$). Funnel plot analysis revealed no publication bias for all subgroup analysis (Figs. 5–7).

DISCUSSION

There is considerable debate regarding the clinical utility of imaging in tendinopathy (Docking et al. 2015). There are two important issues to consider which have led to this debate. The first issue is that in some studies, abnormal structural tendon changes, as seen with US, have been reported in up to 59% of asymptomatic individuals (Brasseur et al. 2004; Cook et al. 1998; Fredberg and Bolvig 2002; Giombini et al. 2013; Hirschmüller et al. 2012; Khan et al. 1997; Leung and Griffith 2008). It is therefore apparent that there is a disparity that can be seen between the findings of imaging and the clinical presentation (Fredberg et al. 2004). Second, although numerous studies have examined the sensitivity and accuracy of imaging in identifying tendinopathy (Docking et al. 2015; Scott et al. 2013), there is a lack of a valid clinical gold standard for diagnosing tendinopathy with which to reliably compare findings (Docking et al. 2015). Additionally, with such a wide

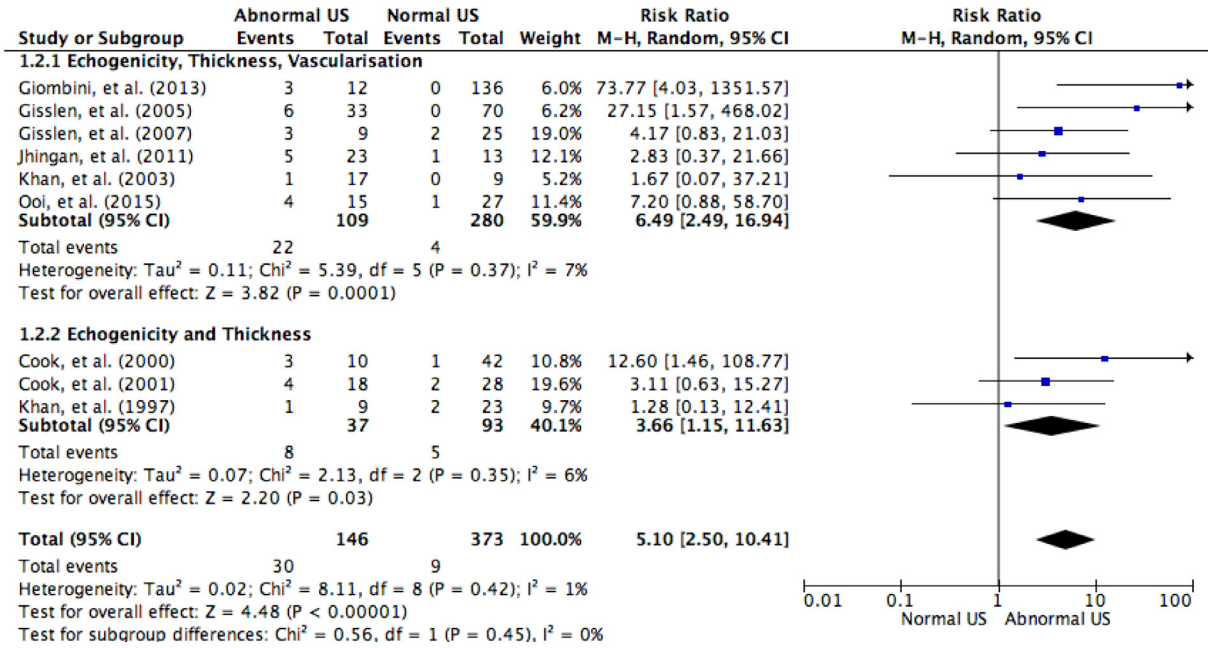

Fig. 3. Meta-analysis results comparing prediction of symptomatic Achilles and patellar tendinopathy using three US-defined parameters and two US-defined parameters. US = ultrasound imaging; CI = confidence interval; M-H = Mantel–Haenszel.

variety of classification systems and different imaging features reported, there appears to be a lack of agreement on an acceptable criterion or classification to match structural changes seen on US with the clinical stages of tendinopathy (Ellis and Manuel 2015). Furthermore, in the clinical setting, sonographers do not appear to use or refer to the continuum model of tendinopathy when diagnosing tendon disorders. Classifying patients according to structural changes, in addition to clinical symptoms, may allow the clinician to direct treatment to the key limiting factors (pain, function or load capacity) (Cook et al. 2016; Scase et al. 2011).

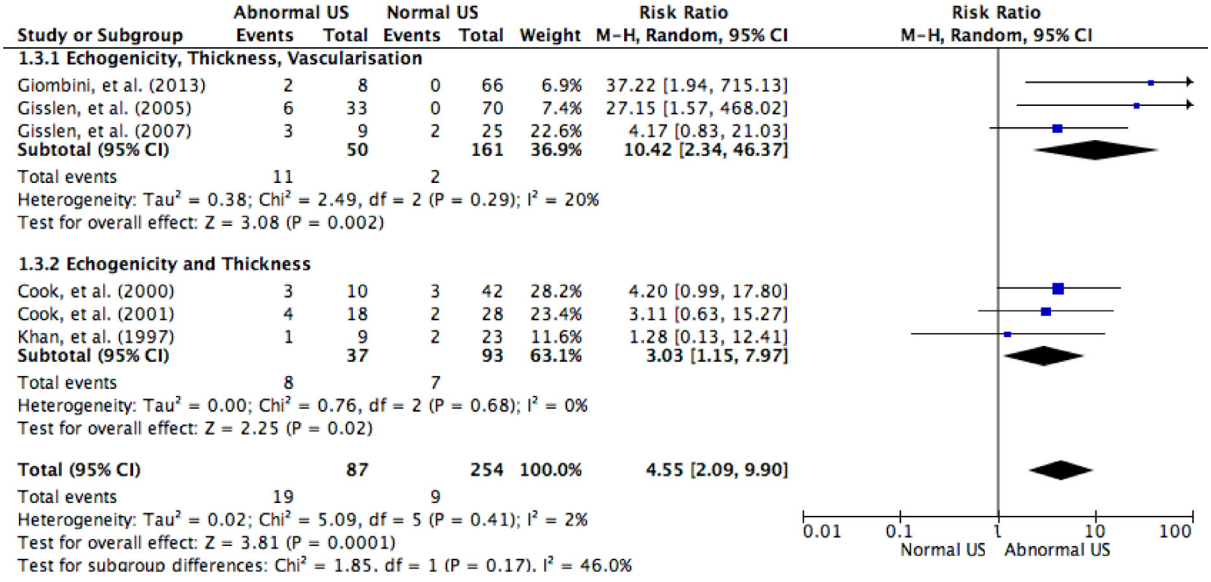

Fig. 4. Meta-analysis results comparing prediction of symptomatic patellar tendinopathy using three US-defined parameters and two US defined parameters.

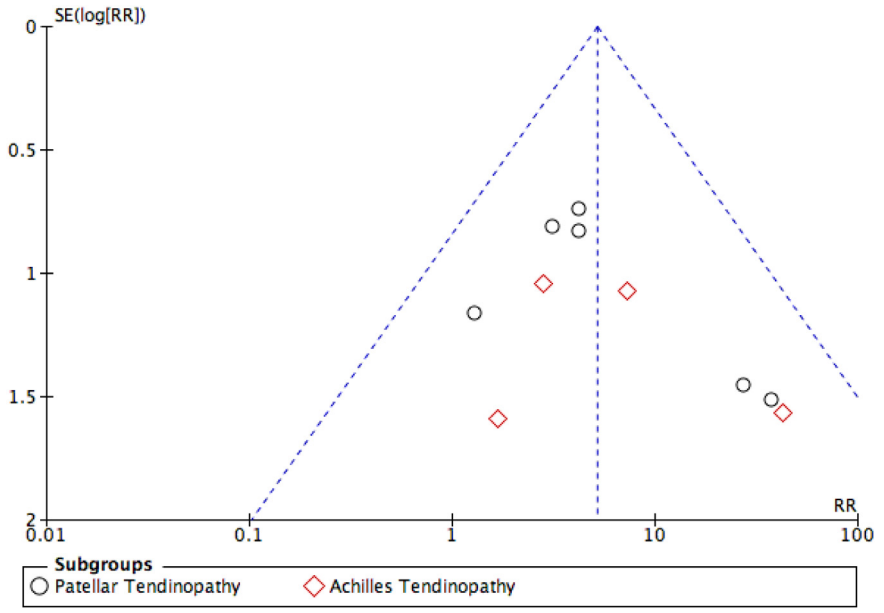

Fig. 5. Funnel plot analysis of study bias for prediction of Achilles and patellar tendinopathy using ultrasound imaging. SE = standard error or the mean; RR = relative risk.

Classification of tendinopathy

The primary aim of this systematic review was to identify the current methods used to classify tendinopathy using US. To the authors' knowledge, this is the first systematic review and meta-analysis to focus specifically on current US parameters used to measure structural change in tendinopathy and the methods of classifying tendinopathy according to these parameters. We found that there is a distinct lack of homogeneity in the criteria used when assessing tendinopathy using US. Although there is significant inconsistency in the currently used US tendinopathy classification methods, common US parameters used to measure structural change can be identified. These results align with those of Ellis and Manuel (2015), who reported significant variability in both the overall classification scales used and

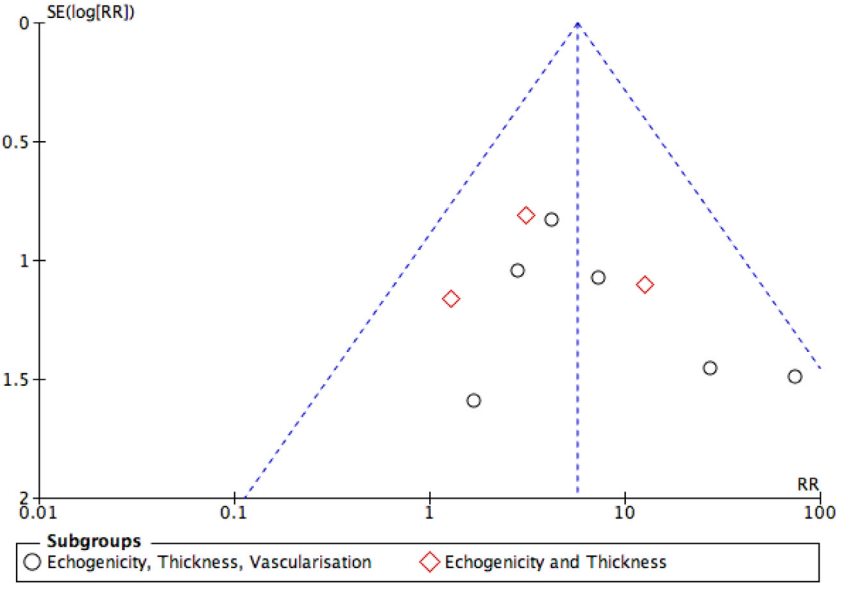

Fig. 6. Funnel plot analysis of study bias for prediction of Achilles and patellar tendinopathy using three US-defined parameters and two US defined parameters. SE = standard error or the mean; RR = relative risk.

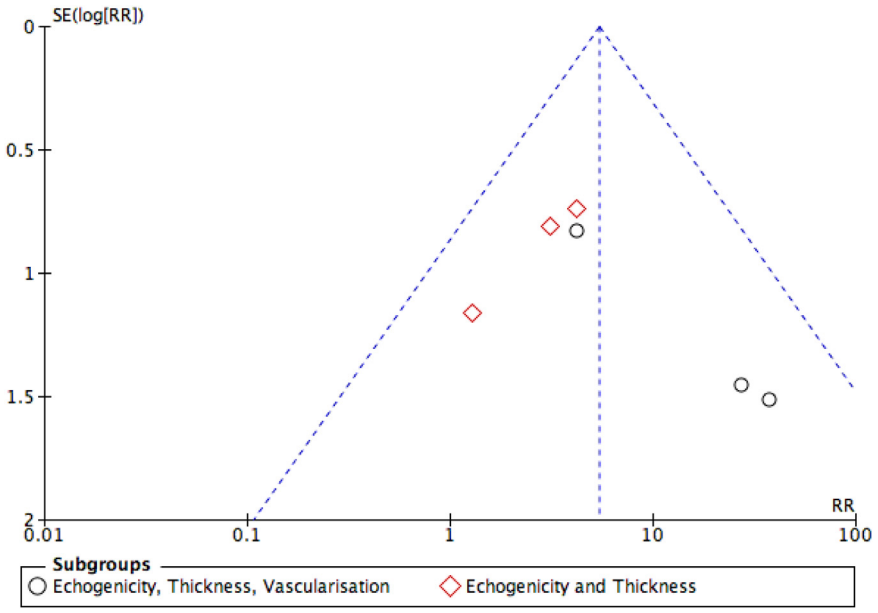

Fig. 7. Funnel plot analysis of study bias for prediction of patellar tendinopathy using three ultrasound imaging-defined parameters and two ultrasound imaging-defined parameters. SE = standard error or the mean; RR = relative risk.

the individual parameters measured from studies that examined tendinopathy with US. Additionally, this review found that there is a lack of a relationship between the classification systems employed clinically and the widely accepted continuum model (Cook and Purdam 2009) of tendinopathy.

Quality of included studies

One of the secondary aims of this literature review was to assess the methodological quality of the literature. According to the previously described quality scoring system and as presented in Table 3, all included studies were determined to be of good methodological quality. The main areas of concern within the methodological quality of included studies were in the minimisation of bias (Comin et al. 2013; Jhingan et al. 2011; Khan et al. 2003; Malliaras et al. 2010), control of confounding factors (Archambault et al. 1998; Comin et al. 2013; Cook et al. 2001a; de Vos et al. 2007; Fredberg and Bolvig 2002; Gisslén and Alfredson 2005; Gisslén et al. 2007; Jhingan et al. 2011; Khan et al. 2003; Malliaras et al. 2010), adequate follow-up (Archambault et al. 1998, Hirschmüller et al. 2012) and presentation of results (Gisslén and Alfredson 2005; Gisslén et al. 2007). Additionally, the main weaknesses of the included randomised controlled trials concerned the recording of dropouts (Fredberg et al. 2008), blinding (de Jonge et al. 2010; Fredberg et al. 2008) and the similarity of treatment and control groups (Fredberg et al. 2008). These results align with those of other systematic reviews (McAuliffe et al. 2016) and provide a methodologically sound base for future research.

Predictive value of US based classification systems

A secondary aim of this review was to assess the predictive value of different US classification methods for the development of future symptoms. Overall, meta-analysis revealed that US-identified tendon abnormalities may present an increased risk (RR = 4.78) for the development of future symptoms in Achilles and patellar tendinopathy. This aligns with the systematic review by McAuliffe et al. (2016), who found that US-identified abnormalities were predictive (RR = 4.97) of the development of symptomatic lower limb tendinopathy. However, further subgroup analysis according to parameters measured revealed significant differences to the predictive value of US. Notably, when measuring tendon matrix changes using US, the number of parameters measured may influence the predictive value of US in asymptomatic patients.

Meta-analysis revealed that compared with using two parameters (echogenicity and thickness; RR = 3.66), including three parameters (echogenicity, thickness and vascularity; RR = 6.49) was more predictive of the development of future symptoms in the lower limb. This was highlighted further when looking at the patellar tendon, for which the RR was considerably higher when using three parameters (RR = 10.49) rather than two parameters (RR = 3.03). These results differ from those of McAuliffe et al. (2016) in that McAuliffe et al.

reported that US-identified abnormalities were a risk factor for the development of tendinopathy in both the Achilles and patellar tendons. However, these results indicated that by utilising more parameters to define tendon abnormalities with US, the RR of developing future clinical tendinopathy may be increased. To the authors' knowledge, this is the first research to investigate the impact of individual US parameters on the predictive value of tendinopathy.

The synthesis of evidence illustrates that there is still debate as to the predictive value of US, with 53% of included studies determining US findings were predictive of future symptoms. Hirschmüller et al. (2012) found that neovascularisation grade 1 may be predictive (odds ratio [OR]: 6.9, 95% CI: 2.6−18.8, $p = 0.0001$) of future symptoms; however, hypo-echogenicity, spindle-shaped thickening and neovascularisation grade 2−3 were not predictive ($p > 0.05$). Comin et al. (2013) reported moderate to severe hypo-echoic regions may be predictive of symptoms in both the patellar and Achilles tendons (Fisher's exact $p = 0.038$). However, intra-tendon defects (patellar $p = 0.166$, Achilles $p = 0.403$) and neovascularisation (patellar $p = 0.342$, Achilles 0.089) were not statistically significant for predicting symptoms. Additionally, Boesen et al. (2012) found no association between pain and abnormal neovascularisation at the end of a volleyball season, with 35% of painful tendons exhibiting abnormal flow. Similarly, de Jonge et al. (2010) reported no significant difference in VISA-A scores between patients with and without neovascularisation at baseline ($p = 0.71$), and de Vos et al. (2007) reported no statistical difference in the predictive value of neovascularisation compared with both VAS ($p = 0.053$) and VISA-A ($p = 0.147$).

Conversely, Fredberg and Bolvig (2002) reported that abnormal US was associated with a 17% risk of developing symptomatic jumper's knee and 45% risk of developing symptomatic Achilles tendinopathy. Similarly, Fredberg et al. (2008) found that an abnormal US had an RR of 2.8 (95% CI: 1.6−4.9, $p = 0.002$) in the Achilles tendon and RR of 2.2 (95% CI: 0.9−5.7, $p = 0.09$) for the patellar tendon. Additionally, Malliaras et al. (2010) determined there was an increased probability of pain in tendons with both hypo-echoic regions (59%) and diffuse thickening (43%). This is supported by Visnes et al. (2015), with both hypo-echogenicity (OR = 3.3, 95% CI: 1.1−9.2) and neovascularisation (OR = 2.7, 95% CI: 1.1−6.5) increasing the risk of developing symptomatic jumper's knee.

This variability in the reported results may be explained by two important factors. Firstly, research utilising US has been limited to classifying tendon structural change with the use of subjective grading scores established on a multitude of pathologic features (Docking et al. 2015; Ellis and Manuel 2015). Objective measurement of tendon structural change, seen with US, has been restricted to measuring dimensions such as tendon diameter, cross-sectional area of the tendon and number or size of hypo-echoic regions (Docking et al. 2015). Secondly, although numerous studies have examined the sensitivity and accuracy of US in identifying tendinopathy (Docking et al. 2015; Scott et al. 2013), there is a lack of a valid clinical gold standard for diagnosing tendinopathy, making assessment of the clinical utility of US difficult (Docking et al. 2015; McAuliffe et al. 2016).

Limitations

The exclusion of grey literature may increase the risk of publication bias (Conn et al. 2003). It is also possible that non-English articles that may have met the inclusion criteria were missed. However, there is no evidence of systematic review bias from language restrictions (Morrison et al. 2012). The exclusion of promising methods of US, such as elastography, may have had an effect on publication bias. However, although early research shows promise as an adjunct to standard US (Ooi et al. 2014), evidence is limited to smaller cross-sectional studies and there are some technical challenges to producing high-quality, reproducible elastograms (Domenichini et al. 2017; Ooi et al. 2014; Ryu and Jeong 2017). Moreover, as elastography is a recent development, many commercial US units lack the ability to assess this feature. A better understanding of fundamental properties of elastography (Ryu and Jeong 2017) and standardisation of imaging protocols (Ooi et al. 2014) may allow future research to incorporate this technique into the US assessment of tendon matrix change. Additionally, study quality was assessed using the CASP tool (Critical Appraisal Skills Programme 2017a, 2017b), which does not utilise a scoring system to grade study quality; thus, one was developed for the purpose of the review. The selection of quality appraisal tool may affect review conclusions (Voss and Rehfuess 2013); however, this was addressed by using two independent reviewers and determining inter-rater agreement for each question on the checklist.

Implications for future research

Given the complexity of the relationship among structure, dysfunction and pain in tendinopathy, there is scope to develop a standardised method to assess tendon structural change on US, incorporating a number of parameters and allowing for greater consistency in the diagnosis of tendinopathy. Based on the results of this systematic review and meta-analysis, future criteria for diagnosing tendinopathy using US should include measures of all three parameters (tendon thickness,

echogenicity and vascularity) when assessing tendon structural change. Furthermore, there is a need for further studies to assess the validity of developing a clinical gold standard for the diagnosis of tendinopathy that incorporates both clinical and US findings to formulate a diagnosis of tendinopathy. Additionally, to better integrate clinical and US findings, there is an opportunity to develop a method that merges the continuum model with US parameters to form an overall criterion that allows for greater consistency in the diagnosis of tendinopathy. By use of the results of this literature review, an ordinal scale may be developed to diagnose tendinopathy using US as "normal," "reactive/early disrepair" or "late dysrepair/degenerative" to better align with the continuum model (Ellis and Manuel 2015; Scase et al. 2011). However, cut-off values would need to be determined to distinguish between the different stages within the continuum.

CONCLUSIONS

This review indicates that there is significant variability in the US-based criteria used to diagnose tendinopathy. Notably, US is predictive of the development of future clinical symptoms. Furthermore, the assessment of tendon structural change using three parameters revealed a higher RR compared with using two parameters, indicating the predictive value of using three parameters. Furthermore, as imaging is one component of the clinical picture, there is scope for future research to develop a standardised criterion that incorporates both clinical and US features to diagnose tendinopathy. This has the potential to improve the monitoring and clinical management of tendinopathies.

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