BJR

SYSTEMATIC REVIEW

Cytokines in tendon disease

A SYSTEMATIC REVIEW

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Objectives

Emerging evidence indicates that tendon disease is an active process with inflammation that is critical to disease onset and progression. However, the key cytokines responsible for driving and sustaining inflammation have not been identified.

Methods

We performed a systematic review of the literature using MEDLINE (U.S. National Library of Medicine, Bethesda, Maryland) in March 2017. Studies reporting the expression of interleukins (ILs), tumour necrosis factor alpha (TNF-α) and interferon gamma in diseased human tendon tissues, and animal models of tendon injury or exercise in comparison with healthy control tissues were included.

Results

IL-1β, IL-6, IL-10, and TNF-α are the cytokines that have been most frequently investigated. In clinical samples of tendinopathy and tendon tears, the expression of TNF-α tended not to change but IL-6 increased in tears. Healthy human tendons showed increased IL-6 expression after exercise; however, IL-10 remained unchanged. Animal tendon injury models showed that IL-1β, IL-6, and TNF-α tend to increase from the early phase of tendon healing. In animal exercise studies, IL-1β expression showed a tendency to increase at the early stage after exercise, but IL-10 expression remained unchanged with exercise.

Conclusions

This review highlights the roles of IL-1β, IL-6, IL-10, and TNF-α in the development of tendon disease, during tendon healing, and in response to exercise. However, there is evidence accumulating that suggests that other cytokines are also contributing to tendon inflammatory processes. Further work with hypothesis-free methods is warranted in order to identify the key cytokines, with subsequent mechanistic and interaction studies to elucidate their roles in tendon disease development.

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Keywords: Tendon, Tendinopathy, Cytokine

Article focus

- To investigate gene and protein expression of cytokines in the development and progression of tendon disease and during tendon healing compared with healthy tendon tissues in both humans and animals.
- To investigate how exercise affects the gene and protein expression of cytokines in tendon tissues.
- To determine how cytokines affect the expression of tendon extracellular matrix (ECM) genes and proteins.

Key messages

- The most frequently investigated cytokines in the development and progression of tendon disease, during tendon healing or in response to exercise were interleukin (IL)-1β, IL-6, IL-10, and tumour necrosis factor alpha (TNF-α), with a paucity of research on others that may also contribute.
- IL-6 was the only cytokine involved in human tendon disease and was increased in tendon tears, whereas IL-1β, IL-6, and TNF-α tended to be increased in animal models of tendon injury.
- The effects of cytokines on the expression of tendon ECM genes and proteins could not be determined due to the lack of studies which, in turn, warrants further investigation.

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Strengths and limitations

- This review encompasses current literature by a systematic review and organises the evidence in human and animal studies separately.
- The key cytokines and their dominant role in the development of tendon disease could not be determined due to the small number and heterogeneity of samples and models.

Introduction

Tendon disease is increasingly common and comprises a third of all musculoskeletal complaints.[1] The tendon tissue of early-stage disease, commonly referred to as tendinopathy, is characterised by the development of fibrosis: disoriented collagen fibres; altered composition of extracellular matrix (ECM) proteins; formation of new vessels; and rounding of tendon cells.[2] The accumulation of fibrotic tissue predisposes to injury and tendon tear.[3,4] The aetiology of tendon disease is acknowledged to be multifactorial, with overuse, trauma, ageing, and genetic predisposition as notable factors;[5] however, the involvement of inflammation has long been debated.[6] Today, emerging evidence indicates a strong inflammatory component to the pathogenesis of tendon disease, with inflammatory cells and cytokines as important regulators of the tendon ECM.[7,8] Cytokines such as interleukins (IL), tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), alongside growth factors such as transforming growth factor beta (TGF-β) and platelet-derived growth factor, are released from tendon stromal and immunoregulatory cells in response to tissue injury, mechanical stress, and malfunction.[3,9,10] They alter the cellular phenotype of the local cells and the persistence of the cellular change by chronic inflammation results in the production of excessive and inappropriate matrix proteins and fibrosis.[10] Similar responses have been widely studied in fibrotic diseases in organs such as the liver, kidney, and lung.[11]

The aim of this study was to systematically review the key cytokines that are involved in the development of tendon disease with a focus on fibrosis. The first objective was to investigate the gene and protein expression of cytokines in diseased tendons along the development of tendinopathy to tear, in comparison with that of healthy tendon. The second objective was to investigate how exercise affects the expression of these cytokines in tendon tissues. We also reviewed how tendon cells respond to these cytokines in the expression of ECM genes and proteins. We hypothesised that the cytokines expressed would vary during the process of tendon disease development or injury healing, and that the tendon cells from normal tissue, early disease, late disease, and healing would have differential responses to these cytokines.

Materials and Methods

This systematic review was designed, undertaken, and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Scientific literature was obtained using the MEDLINE (U.S. National Library of Medicine, Bethesda, Maryland) electronic database using the term "tendon AND cytokine" in March 2017.

The studies were included if they reported the expression of ILs, TNF-α, and IFN-γ as these were found to be the cytokines that were consistently considered through the preliminary screening. The cytokines of the TGF-β superfamily were excluded as we have reviewed these previously.[12] Studies that compared the expression of the cytokines in diseased human tendon tissues and animal models of tendon injury or exercise with that of healthy control tissue were included. The tendon tissues included in the search criteria were from the mid-substance of tendon or tendon-to-bone enthesis. Studies on muscle-tendon junctions and ligament reconstruction using tendon grafts and other soft tissues (muscles, ligaments, cartilage, fat, bursa, and synovial tissues), as well as fetal, knockout animal models, animal studies of endocrine disorders (hyperglycaemia, menopause), and *ex vivo* experimental studies were excluded. The *in vitro* studies that investigated the effects of the cytokines on the expression of tendon ECM genes and proteins (collagens, elastin, proteoglycans, metalloproteinases (MMPs), tissue inhibitor of metalloproteinases (TIMPs), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)) by healthy, diseased, or injured tendon cells were also included. Review articles, protocols, commentaries, case reports, and studies that were not reported in English were excluded. There was no limitation as to the year of publication.

Our search yielded 784 results. One article was identified by searching through references of listed articles. Following title screening, 594 abstracts were screened to determine eligibility and 57 papers met the inclusion criteria (Fig. 1). The papers that met the criteria are summarised in the additional files (supplementary tables i to iii).

Study characteristics. The studies that compared the expression of cytokines in diseased human tendons obtained tissue samples from healthy, tendinopathic, torn, and healing tendons after surgical repair of the rotator cuff (RC), Achilles, patella, posterior tibialis, digital flexors, and extensor carpal radialis brevis. The effect of exercise was studied in the Achilles and patellar tendons. Five out of 17 studies on human tendon tissues used a gene micro or cytometric bead array to determine the cytokines of interest in diseased human tendon tissues (supplementary table i).

The animal tendon injury models were wide-ranging, using the Achilles, RC, or flexor digitorum (FD) tendons in rats, dogs, and rabbits, with injuries created by

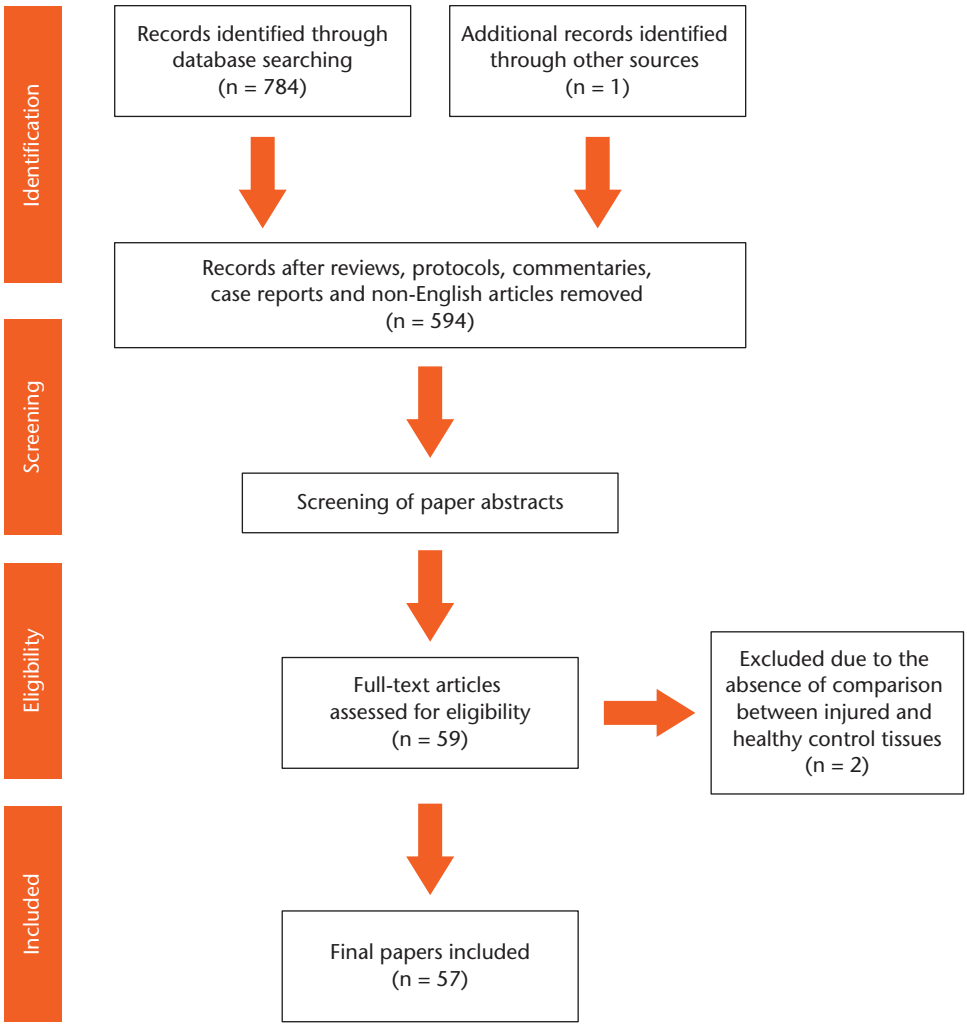

Fig. 1

Flowchart of the systematic review protocol.

collagenase, crush injury, partial transection, and full transection. Depending on the study, the transected tendons were repaired surgically or left to heal spontaneously. The animal tendon exercise models used the patellar, Achilles, RC, or FD tendons of rats or rabbits. Studies on horse tendon tissues obtained clinical samples of FD tendinopathy and compared the expression of cytokines with that of healthy tendon tissues. There were three out of 30 animal studies that used an array to determine the cytokines involved (supplementary table ii).

The *in vitro* studies investigated the effects of cytokines on the expression of tendon ECM genes and proteins in healthy, disease, or injured human and animal tendons. Human tendon cells were obtained from normal or tendinopathic tendons. The anatomy and species differed in all of the studies using animal tendon cells, which included healthy horse FD, injured mouse Achilles, and both healthy and injured rat patellar tendons (supplementary table iii).

Study methodology and assessing the risk of bias. The quality of study methodology was assessed in all papers by referring to the modified scoring system by Dean et al[8] and Morita et al[12] in order to highlight the studies with a high risk of potential bias. The median score was 8 (interquartile range, 7 to 9) out of 10 (supplementary table iv). Eight human tissue studies, six animal model tissue studies, and five *in vitro* experiment studies did not fully describe the age and gender of the included subjects. All of the included studies clearly described the control group. One study obtained the control tissue from the unaffected region of the tendinopathic tendon under confirmation by ultrasonography. There were three studies that sampled diseased tissues based on gross inspection, which may be a risk of bias. All except four studies clearly described the experimental procedures of tissue sampling and analysis, and 32 documented the validity or reliability of the methods used. Seven studies did not use quantitative measures or statistical analysis for comparison. Of the 51 studies that used quantitative analysis

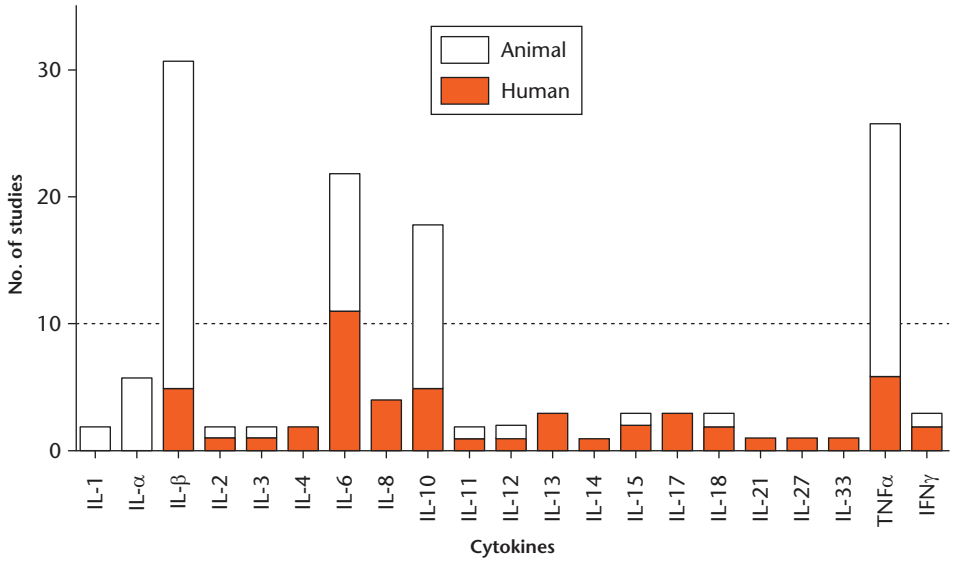

Fig. 2

Number of studies of human tendon tissues and animal tendon injury or exercise models for each cytokine.

with statistical comparison, 45 stated the statistical level of significance, but only eight checked the data for normal distribution. Study limitations were not addressed in 21 studies. A meta-analysis was not carried out due to the heterogeneity of the data from clinical samples and animal models.

Results

A total of 20 cytokines were implicated in the development of tendon disease, healing or in response to exercise: IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-17, IL-18, IL-27, TNF-α, and IFN-γ were identified by array-based studies (seven studies); and IL-21 and IL-33 were guided by literature. IL-1β, IL-6, IL-10, and TNF-α had been investigated in numerous (more than ten) hypothesis-free and literature-guided studies (Fig. 2). Hence, the results on these four cytokines were summarised (Table I). Results of other cytokines are summarised in the additional files (supplementary table v). Effects of cytokines on the expression of tendon ECM genes and proteins in tendon cells have been presented for IL-1β, IL-6, IL-10, and TNF-α, similarly (Table II). Results of other cytokines are shown in the additional files (supplementary table vi).

IL-1β. In clinical samples, gene expression was decreased and protein expression increased in torn RC, but it remained unchanged in torn Achilles tendon tissues and after repair, exercise, or tendinopathy.[13-17] The role of IL-1β in human tendon disease or after exercise could not be concluded. In animal injury models, gene and protein expression of IL-1β tended to increase at the early stages of tendon injury or healing until two weeks after the intervention.[18-25] Similarly, exercise tended to increase the gene and protein expression of IL-1β in the early stages.[26-38] Treatment of tendon cells with IL-1β showed catabolic effects such as increased expression of matrix metalloproteinase (MMPs), with a significant difference between cells from healthy and injured patellar tendons.[39]

IL-6. Gene and protein expression of IL-6 tended to be increased in RC and Achilles tendon tear patient samples,[40-42] which continued until two weeks post-surgical repair,[16] but not in patients with Achilles, RC, or posterior tibialis tendinopathy.[17,41-43] Increased IL-6 protein expression was noted after prolonged running in healthy tendons,[44,45] but not in tendinopathic Achilles tendons.[14] In animal injury models, gene, and protein expression of IL-6 was increased from two hours to four weeks after the intervention.[18,19,21,26,46] The effect of exercise was inconsistent in animal models.[26,27,36,38,40] IL-6 treatment on tendon cells did not have any effect on the expression of tendon ECM genes and proteins.[47]

IL-10. The expression of IL-10 was inconsistent in clinical samples[13,14,16,17,41] and animal injury models.[18,20,21,46,48,49] No effects of exercise on the expression of IL-10 were noted in either humans or animals.[26,32,34,36,38] IL-10 treatment on tendon cells did not have any effect on the expression of tendon ECM genes and proteins.[47]

TNF-α. Gene and protein expression of TNF-α tended not to change in clinical samples of RC and Achilles tendinopathy and tear patients.[16,40,41,50] The effect of exercise on the expression of TNF-α in healthy human tendons has not been reported. In animal injury models, gene expression of TNF-α was elevated from two hours to nine days and declined at two weeks after the intervention,[19,20,21,25,51] whereas the protein expression increased after four days. The effect of exercise on the gene and protein expression of TNF-α was inconclusive in animal models.[26,31,32,34-38] The effects of TNF-α on tendon cells could not be concluded as genes of interest differed between studies.[47,52]

Table I. Expression of interleukins IL-1β, IL-6, IL-10, and tumour necrosis factor alpha (TNF-α) in tissues of diseased human tendon, animal models of tendon injury or exercise *versus* healthy control tendon. Arrows indicate increased (↑), unchanged (→), or decreased (↓) expression of cytokines in tissues of diseased human tendon, animal models of tendon injury or exercise *versus* healthy control tendon. If two arrows are given, this indicates that more than one change in expression has been reported (for example, →/↑ indicates that both unchanged and increased expression have been reported)

Cytokine	Animal	Disease model	Increased, unchanged, decreased in diseased *vs* control	
			Gene	**Protein**
IL-1β	Human	Rotator cuff, tear	↓[13]	↑ (descriptive)[15]
		Achilles, tear, post-operative (2 wks)		→[*16]
		Achilles, tendinopathy		→[*17]
		Achilles, tendinopathy + exercise (1 hr run)	→[†14]	
	Rat	Rotator cuff, tendinopathy model, transection + repair		↑ (1 wk)[60]
		Achilles, partial transection		↑ (1 day) → (4 days)[20]
		Achilles, transection + repair	↑ (3 days; 1, 2, 4 wks)[18]	
		Achilles, crush		↑ (1 day)[21,22] → (3 days)[22] ↑ (5 days)[51] ↑ (1 wk)[22]
		Achilles, collagenase	↑ (1, 2 wks)[19]	
		Achilles, exercise	→ (7 wks)[27]	
		Achilles, transection + exercise (post-operative day 5)	↑ (1, 3 hrs) → (12 hrs)[28]	
			↑ (1, 3 hrs) → (12 hrs)(IL-1RA)[28]	
		Achilles/patella, stress deprivation		↑ (2, 6 wks)[31]
		Patella, cyclic exercise by surgery	↑ (high strain) ↓ (low strain)[29]	↑ (high strain) ↓ (low strain)[29]
		Flexor digitorum, exercise		↑ (training)[26] →/↑ (3, 6, 8 wks)[32-36] → (9 wks)[36] →/↑ (12 wks)[33,36-38] → (18, 24 wks)[26]
	Rabbit	Rotator cuff, partial transection (defect)	↑ (1, 3 days; 1 wk) → (3 wks) (descriptive)[23]	↑ (1, 3 days; 1 wk) → (3 wks)[23]
		Flexor digitorum superficialis, transection + repair	↑ (3, 6 days) → (12, 24 days)[24]	
		Flexor, electrical stimulation	→ (14 wks)[30]	
	Dog	Flexor, transection + repair	↑ (1, 3, 9 days)[25]	
	Horse	Flexor digitorum superficialis, tendinopathy		↑ (descriptive)[61]
IL-6	Human	Rotator cuff, tear	↑[40] →[41]	↑[40]
		Rotator cuff/Achilles/patella/biceps/ECRB/flexor, tear	↑ (OSM)[62] ↓ (IL-6R)[62]	
		Rotator cuff/posterior tibialis, tendinopathy	→ [41,43] → (IL-6, OSM, LIF, IL-6R)[42]	
		Achilles, tear	↑ (IL-6, OSM, LIF)[42] ↓ (IL-6R)[42]	
		Achilles, tear, post-operative (2 wks)		↑[*16]
		Achilles, tendinopathy	↑ [42] → [43] ↓ (IL-6R)[42] → (OSM, LIF)[42]	→[*17]
		Achilles, exercise (1 hr/36 km run)		↑[*] (post-exercise 2-6 hrs; 1, 2 days)[44,45]
		Patella, exercise (knee strenuous extension)		→ (post-exercise 1, 3 days)[*63]
		Achilles, tendinopathy + exercise (1 hr run)	→[†14]	
	Rat	Rotator cuff, exercise	↑ (4 wks)[40]	
		Achilles, transection + repair	↑ (3 days; 1, 2, 4 wks)[18]	
		Achilles, crush		↑(1 day)[21]
		Achilles, collagenase	↑ (2 hrs)[46] ↑ (1, 2 wks)[19]	
		Achilles, exercise	→ (7 wks)[27]	
		Flexor, exercise		↑ (training)[26] → (3, 6 wks)[36] ↑ (9 wks)[36] →/↑(12 wks)[36,38] → (18 wks)[26] ↑ (24 wks)[26]
IL-10	Human	Rotator cuff, tear	↑[13] → [41]	
		Rotator cuff/Achilles, tendinopathy	↓[41]	↑ (descriptive)[*17]
		Achilles, tear, post-operative (2 wks)		↑[*16]
		Achilles, tendinopathy + exercise (1 hr run)	→[†14]	
	Rat	Achilles, partial transection		→ (1, 4 days)[20]
		Achilles, transection + repair	→ (3 days; 1, 2 wks) ↑ (4 wks)[18]	
		Achilles, crush		→ (1 day)[21]
		Achilles, collagenase	↑ (2 hrs)[46] → (1, 2 wks)[48,49]	
		Flexor digitorum, exercise		→ (training, 3, 6, 8, 9, 12, 18, 24 wks)[26,32,34,36,38]
TNFα	Human	Rotator cuff, tear	→[40] ↑[41] ↓ (TNFR1)[13]	
		Rotator cuff/Achilles tendinopathy	→[41]	→(TNFα, TNFR2) ↑ (TNFR1)[50]
		Achilles, tear, post-operative (2 wks)		→[*16]
		Achilles, tendinopathy + exercise (1 hr run)	↓[†14]	
	Rat	Rotator cuff, tendinopathy model, transection + repair		→ (1 wk)[60]
		Rotator cuff, exercise	↑ (4 wks)[40]	
		Achilles, partial transection		→ (1 day) ↑ (4 days)[20]
		Achilles, crush		→ (1 day)[21] ↑ (5 days)[51]

(Continued)

Table I. (Continued)

Cytokine	Animal	Disease model	Increased, unchanged, decreased in diseased *vs* control	
		Achilles, collagenase	↑ (2 hrs)[46,64] ↑ (1 wk) → (2 wks)[19]	
		Patella, stress deprivation		↑ (2, 6 wks)[31]
		Flexor, exercise		↑ (training)[26,34] → (3, 6 wks)[32,34,36] ↑ (8 wks)[34,35] → (9 wks)[36] ↓/→/↑ (12 wks)[34,36-38] → (18 wks)[26] ↑ (24 wks)[26,34]
	Dog	Flexor, transection + repair	↑ (1, 3, 9 days)[25]	
	Horse	Superficial flexor digitorum, tendinopathy	↑ (acute) ↓ (chronic) (descriptive)[65]	↑ (acute) ↓ (chronic) (descriptive) (TNFα, R1, TRAF2)[65] ↑ (descriptive)[61]

*studies that obtained clinical samples of tendon by microdialysis
†studies that sampled control tissues from the healthy region of the same tendon
IL-1RA, interleukin-1 receptor antagonist; OSM, oncostatin M; IL-6R, interleukin 6 receptor; LIF, leukemia inhibitory factor; TNFR, tumour necrosis factor receptor; TRAF, TNF receptor-associated factor; ECRB, extensor carpi radialis brevis

Table II. Cellular responses to treatment by cytokines in tendon cells. Arrows indicate increased (↑), unchanged (→), or decreased (↓) expression of cytokines in tissues of diseased human tendon, animal models of tendon injury or exercise *versus* healthy control tendon

Treatment	Cells	Increased, unchanged, decreased in response to treatment *versus* control	
		Gene	**Protein**
IL-1β	Human, various, normal	Collagen I ↓ MMP1 ↑ MMP2 → MMP3 ↑ MMP13 ↑ TIMP1 → TIMP2→ ADAMTS-4 →[66,67]	MMP1 ↑ MMP3 ↑[67]
	Human, not described, tendinopathy	MMP1 ↑ MMP2 → MMP3 ↑[68]	MMP1 ↑ MMP2 ↑ MMP3 ↑[68]
	Rat, patella, normal	MMP13 ↑*[39]	
	Rat, patella, injured	MMP13 ↑*[39]	
	Mouse, Achilles, injured	Collagen I ↓ Collagen III ↓ Biglycan ↓ Decorin ↑ Fibromodulin ↓ Lumican → Aggrecan ↓ MMP13 ↑[69]	
IL-6, IL-10	Human, various, normal	Elastin → MMP1 →[47]	Collagen I →[47]
TNFα	Human, various, normal	Elastin ↑ MMP1 ↑[47]	Collagen I ↓[47]
	Horse, FDS, normal	Collagen I ↑ MMP9 → MMP13 ↓[52]	

*significant difference between tendon cells from normal and injured patellar tendons ($p < 0.05$)
IL, interleukin; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; TNF, tumour necrosis factor; FDS, flexor digitorum superficialis

Discussion

This systematic review shows that IL-1β, IL-6, IL-10, and TNF-α are the most frequently investigated cytokines in the development and progression of tendon disease, during tendon healing and in response to exercise. Most studies focused on inflammatory cytokines based on previous literature, and only a few studies used hypothesis-free approaches to define the implicated cytokines.

Expression of IL-1β, IL-6, IL-10, and TNF-α differed depending on the stage of the tendon disease development, injury healing, and in response to exercise: IL-1β tended to increase in the early stage of tendon injury or exercise in animal models; IL-6 was suggested to increase at tendon tear, after prolonged exercise in healthy human tendons, and in the early stage of tendon injury in animal models; IL-10 remained unchanged in response to exercise in both humans and animals; and TNF-α tended to increase in the early stage of animal tendon injury models. Their functional mechanism in tendon disease development or healing could not be determined due to the small number of studies. The cellular response to IL-1β treatment significantly differed between injured and healthy tendon cells, but the involvement of other cytokines in tendon disease, healing, or after exercise could not be determined due to the paucity of studies or the inconsistency of the results thus far.

We were not able to identify the key cytokines through array studies alone due to the small number of studies, and due to the heterogeneity of clinical samples and animal models. An arbitrary number of more than ten studies was set to focus on the cytokines that had been investigated frequently in the literature. However, there was a wide variety of the anatomical locations of the diseased and control tendons, diagnostic criteria of tendinopathy, intervention, and the methods of gene or protein expression analysis in both human and animal studies. Tendons respond differently despite similar intervention based on anatomical location, function,[53] and the content of exercises.[37] Variances of the study limited the performing of a meta-analysis.

Schulze-Tanzil et al[3] and Millar, Murrell, and McInnes[54] have indicated through narrative reviews that multiple cytokines such as IL-1β, IL-4, IL-6, IL-13, IL-15, IL-17, IL-18, IL-21, IL-33, and TNF family members alongside TGF-β contribute to the development of tendon disease. By carrying out a systematic review, we captured all current literature and organised the evidence in human and animal studies separately. This largely supported the data presented in previous narrative reviews. Animal studies have been helpful in understanding tendon healing and the effect of exercise, but only represent limited features of the pathophysiology and clinical diseases.[55] Our data

on the four most investigated cytokines suggest that the expression of cytokines in diseased human tendons and animal models does not act in the same manner.

Numerous cytokines have been proposed to contribute to the development of tendon pathology, but there is a clear shortage of analyses on human-derived tendon tissue and cells. There is a risk of noting IL-1β, IL-6, IL-10, and TNFα as the key cytokines in tendon disease just for their frequent investigation. More work is warranted through individual interrogation to specify the cytokines that actually play prominent roles. Dakin et al[41] indicated that advanced-stage disease tendon tissues from large to massive tears have a tissue inflammation signature characterised by the activation of signal transducer and activator of transcription 6, which is predominantly activated by cytokines such as IL-4. Millar et al,[56,57] through mechanistic studies, have proposed IL-33 as an alarmin that triggers inflammation and IL-17A as an inflammatory modulator regulating cytokines, which contribute to the development and progress of tendon disease. There is clearly a strong inflammatory component in the development of tendon disease, with cytokines, which thus far have not been investigated frequently, potentially playing a substantial role. In the case of rheumatoid arthritis, TNF-α unexpectedly turned out to be the master regulator of the pro-inflammatory cytokines contributing to the disease.[58] Moreover, it may also be important to consider interplay of numerous inflammatory processes with regard to different cell types, receptors, and biological and physical environments, and not just to focus on a limited number of molecules.

The cellular response of tendon cells to cytokines in the expression of tendon ECM genes differed depending on cell phenotype. A study by Tohyama et al[39] suggested that infiltrating fibroblasts show significantly decreased expression of an ECM gene (MMP13) in response to IL-1β treatment when compared with the response of healthy tendon cells, and this comes in line with the studies by Dakin et al[41,59] reporting that diseased tendon stromal cells may be primed for inflammation. Although the directions of the stimulatory or inhibitory effect of IL-1β in the gene and protein expression of collagens and MMPs were similar, it should be noted that the magnitude of the change may differ in cells isolated from diseased or healing tissues in comparison with healthy cells.[59] Currently, only a few studies have focused on the mechanisms of action of the cytokines in cells derived from tissues of different phenotypes.

Determining both the temporal expression of cytokines during tendon disease progression and the mechanism of interaction of tendon cells with focus on cell phenotype is essential in order to improve our understanding of tendon disease pathophysiology and tendon healing. A systematic approach using well-defined clinical specimens to identify the cytokines that play a prominent role in the development of tendon disease is warranted. Further mechanistic studies on cytokine biology based on context of expression and surrounding inflammatory milieu should conduce identification of fundamental therapies to improve disease management through enhancing the quality of tissue repair or slowing disease progression.

Supplementary material

Tables and figures showing the main characteristics of the papers included, results of assessment of study methodology quality, and summarised data of the expression of other cytokines in tendon tissues are available alongside the online version of this article at www.bjr.boneandjoint.org

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Author Contribution
- W. Morita: Study concept and design, Data collection, Analysis, Interpretation of data, Drafting the manuscript.
- S. G. Dakin: Analysis, Interpretation of data, Critical revision of manuscript.
- S. J.B Snelling: Analysis, Interpretation of data, Critical revision of manuscript.
- A. J. Carr: Supervision of study, Interpretation of data, Critical revision of manuscript.

Conflict of Interest Statement
- None declared