Proteomics Perspectives in Rotator Cuff Research: A Systematic Review of Gene Expression and Protein Composition in Human Tendinopathy

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Abstract

Background
Rotator cuff tendinopathy including tears is a cause of significant morbidity. The molecular pathogenesis of the disorder is largely unknown. This review aimed to present an overview of the literature on gene expression and protein composition in human rotator cuff tendinopathy and other tendinopathies, and to evaluate perspectives of proteomics – the comprehensive study of protein composition - in tendon research.

Materials and Methods
We conducted a systematic search of the literature published between 1 January 1990 and 18 December 2012 in PubMed, Embase, and Web of Science. We included studies on objectively quantified differential gene expression and/or protein composition in human rotator cuff tendinopathy and other tendinopathies as compared to control tissue.

Results
We identified 2199 studies, of which 54 were included; 25 studies focussed on rotator cuff or biceps tendinopathy. Most of the included studies quantified prespecified mRNA molecules and proteins using polymerase chain reactions and immunoassays, respectively. There was a tendency towards an increase of collagen I (11 of 15 studies) and III (13 of 14), metalloproteinase (MMP)-1 (6 of 12), -9 (7 of 7), -13 (4 of 7), tissue inhibitor of metalloproteinase (TIMP)-1 (4 of 7), and vascular endothelial growth factor (4 of 7), and a decrease in MMP-3 (10 of 12). Fourteen proteomics studies of tendon tissues/cells failed inclusion, mostly because they were conducted in animals or in vitro.
Conclusions

Based on methods, which only allowed simultaneous quantification of a limited number of prespecified mRNA molecules or proteins, several proteins appeared to be differentially expressed/represented in rotator cuff tendinopathy and other tendinopathies. No proteomics studies fulfilled our inclusion criteria, although proteomics technologies may be a way to identify protein profiles (including non-prespecified proteins) that characterise specific tendon disorders or stages of tendinopathy. Thus, our results suggested an untapped potential for proteomics in tendon research.

Introduction

Tendinopathy may be understood as a clinical diagnosis designating tendon pain, which is often associated with tendon swelling and intratendinous changes[1]. Often, tendinopathy is used synonymously with tendinitis and tendinosis, but the last-mentioned terms may also be reserved for tendons with histopathologic findings[1]. Tendon specimens from humans and animals with tendinopathy often show histopathologic changes, which may precondition the tendon to rupture[2–5]. Clinical manifestations suspected to reflect rotator cuff tendon alterations (e.g. subacromial impingement syndrome) occur with a prevalence of 2–8% in general population samples[6–8], and increasing rates of subacromial decompression surgery have been reported[9–11]. Most likely, tendinopathy results from an interplay between intrinsic and extrinsic factors[12]. Intrinsic factors such as genetic polymorphisms[13–16], hypoxia[17], and apoptosis[18, 19] have been implicated together with extrinsic factors such as micro trauma [20, 21] and occupational biomechanical exposures[22, 23].

Tendon tissue research may be conducted at histological or molecular level. Histology refers to the microscopic study of tissues, whereas molecular studies focus on genes, transcripts, and proteins. Studies of genes give insights into factors, which may predispose individuals to tendon disorders, but the information is static. Studies of transcripts, on the other hand, provide information about current gene expression. Transcripts refer to messenger RNA (mRNA) produced by transcription of DNA and are usually detected using specific DNA probes or RNA primers. However, transcripts are poor indicators of protein levels because the resulting proteins may be modified or degraded, or accumulate in the extracellular matrix (ECM). Proteins in tendons are usually detected and quantified by means of specific antibodies. Due to their reliance on specific probes, primers, and antibodies, analyses of transcripts and traditional analyses of proteins do not allow identification of unexpected molecules.

The completion of the Human Genome Project in 2003 (www.ornl.gov/hgmis) enabled the emergence of OMICS technologies, which deal with the global characterisation of biological systems[24, 25]. OMICS classically includes genomics, transcriptomics, proteomics, and metabolomics, in order of increasing complexity of investigation (S1 Fig)[26]. Proteomics is the comprehensive study of protein composition, while metabolomics aims to explore metabolic activity via quantification of metabolites (including proteins). Proteomics and metabolomics primarily employ mass spectrometry (MS) in combination with bioinformatics.

MS-based proteomics identifies and quantifies proteins without a need for antibodies[25]; in a single specimen, hundreds of proteins may be identified and quantified. This technology has proved useful to identify candidate disease biomarkers and to generate novel hypotheses of disease mechanisms, most notably in cancer research[27]. In recent years, proteomics
technologies have also found use in studies of musculoskeletal disorders, e.g., studies of osteoarthritic cartilage[28–31].

Based on a systematic review of the literature on gene expression and protein composition in human rotator cuff tendinopathy and tendinopathy in other anatomical regions, we aimed to evaluate perspectives of proteomics for progress in tendon tissue research. We expected that several proteins, including several MMPs, collagens, proteoglycans, and proinflammatory cytokines would be differentially expressed/represented in tendinopathy, and with regard to the rotator cuff, especially in case of tears. Molecular characterisation of protein profiles of different tendon disorders or stages of progression of tendon alterations may lead to a more thorough understanding of pathological pathways involved in tendon damage and thereby enable more efficient prevention, early diagnosis, and individualised treatment strategies.

Materials and Methods

We conducted a systematic review in as close accordance with the PRISMA guidelines as possible, given the fact that the review does not evaluate healthcare interventions (the PRISMA checklist is included as S1 Appendix). We have not registered a protocol for the review.

Literature search

A comprehensive, structured search was conducted in Medline, Embase, and Web of Science covering the period from 1 January 1990 to 18 December 2012. In Medline, we used the following search string: (((matrix metalloproteinase* OR scleroprotein* OR cytokine* OR neuropeptide* OR glycoprotein* OR proteoglycan*) NOT medline[sb]) OR cytokines OR inflammation OR scleroproteins OR matrix metalloproteinases OR glycoproteins OR proteoglycans OR neuropeptides OR extracellular matrix proteins OR proteome OR proteomics OR RNA OR gene expression OR proteins) AND ((tendon injur* NOT tendon injuries[MeSH]) OR tendon injuries) OR ((tendinopathy OR ((tendino* OR tendini* OR tendon*) NOT medline[sb]))) OR (tendon AND (lacerations OR rupture)) OR rotator cuff tear OR Achilles tendon tear OR patellar tendon tear) AND humans) NOT review[sb]. Corresponding searches were performed in Embase and Web of Science (S2 Appendix). To focus specifically on proteomics research, we performed an additional specific search in Medline (S3 Appendix). Duplicates were removed and reference lists of retrieved articles were scanned for relevant articles missed by the original search.

Study selection

The review was restricted to original articles in peer-reviewed journals, published in English, Danish, Norwegian, or Swedish. We selected human studies reporting on differential gene expression (mRNA) or protein composition in tendinopathy and/or tendon tears as compared to live or cadaveric controls using control tendon tissue from the same patient and joint (paired samples), healthy tendon tissue from other patients, but the same joint, or from different joints than the patient samples. In addition to studies, which examined gene expression and protein composition in rotator cuff or biceps tendinopathy, we included corresponding studies of Achilles, patellar, and posterior tibial tendinopathy because we expected the biological mechanisms involved in the pathogenesis of these disorders to be similar to those of rotator cuff and biceps tendinopathy[32, 33].

Studies using only cultivated cells, dialysate, or synovial, bursal, or capsular specimens were excluded, together with studies, which did not objectively quantify the outcomes. We also excluded studies, which did not use control tendon tissue. We excluded articles stepwise based firstly on title, secondly on abstract, and thirdly on full text.
Data extraction

Papers were categorised according to their focus on transcripts (including transcriptomics), proteins (including proteomics), or both. We extracted information on first author, publication date, sample size, characteristics of study population, laboratory methods, number and names of transcripts/proteins searched for/identified, and direction of change. Data was extracted by the first author and crosschecked by a co-author (SWS or PF), and central information was presented in table form.

Assessment of methodological quality

Methodological quality was assessed based on a set of 13 criteria modified from a checklist for assessing quantitative studies, where a single research question is not defined a priori (Table 1 and S4 Appendix)[34]. In our quality assessment, we rated studies that used paired samples from the same patient and joint or healthy tendon tissue from other patients, but the same joint, as controls higher than studies that used control tissue from different joints than the patient samples or from cadavers because there is a risk of bias due to regional anatomical differences or post-mortem changes. Total quality scores were calculated as percentages of the maximum possible scores. We considered a quality score >75 as indicative of good methodological quality.

The first author applied the checklist to all articles and consulted two co-authors (SWS and PF) in case of doubt (n = 3). Please note that the articles were only scored with regard to end points relevant to this paper.

Assessment of publication bias

We plotted the direction of change of the most commonly examined MMP (MMP-3) against study size (number of patient samples), and visually inspected the plot for signs of publication bias. Inspired by the rationale behind funnel plots[35], the idea was that smaller studies would be more likely than larger studies to remain unpublished if the results pointed to a change in an unexpected direction.

Results

The primary searches yielded 2199 articles, of which we excluded 2097 based on title or abstract and 48 after full-text reading (a list of these 48 articles and reasons for their exclusion can be found in S5 Appendix). Of the 54 included articles, 25 dealt with rotator cuff or biceps tendinopathy[17, 18, 36–58], 14 with Achilles tendinopathy[33, 59–71], 3 with posterior tibial tendinopathy[72–74], 9 with patellar tendinopathy[75–83], 1 with both Achilles and patellar tendinopathy[84], 1 with both Achilles tendinopathy and posterior tibial tendinopathy[85], and 1 with pooled tendinopathic tissue from various anatomical locations[86]. Fig 1 displays the flow diagram of the inclusion process. Table 2 summarises characteristics and findings of rotator cuff and biceps studies. S1–S3 Tables show corresponding information regarding other tendons. In total, the 54 included articles comprised 975 specimens representing tendinopathy with or without tears and 508 control samples, and they explicitly evaluated the expression/representation of more than 140 prespecified transcripts and proteins. Table 3 shows experimental techniques used for the analysis of gene expression and protein composition. The predominant laboratory methods were real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) to detect and quantify mRNA, and Western blots and immunohistochemistry to detect and quantify proteins; only two studies used micro arrays.
Studies were fairly evenly distributed across study types; about a third focused on gene expression (mRNA), a third on protein representation, and a third on both gene expression and protein representation. In our additional specific Medline search, we identified 13 proteomics studies, of which 5 [87–91] had not been captured in the comprehensive searches. Altogether we identified 14 studies that applied proteomics technologies on tendon tissues/cells, but none of them were eligible for inclusion in the present review: 1 study was only presented as a conference abstract [92], 10 were conducted on animal tendons or cultured cells [88, 90, 91, 93–99], and 3 were conducted on human tendons to examine exercise-induced changes [100], drug concentrations [101], or laboratory procedures [102].

Quality assessment

Quality scores are listed in Table 2 and S1–S3 Tables. Details are presented in S6 Appendix. No study achieved the maximum quality score; however 56% scored >75. Major reasons for lower scores were poor comparability between tendinopathy/tear samples and control samples, primarily with respect to age, a scarcity of healthy tendon control samples especially in studies of rotator cuff tendons, lacking validation of results against other methods, and blinding of examiners to disease state. Furthermore, many studies failed to specify inclusion criteria.

Surgical specimens and control tissue

Studies of rotator cuff tendinopathy relied predominantly on surgical specimens from degenerated or torn supraspinatus tendons compared with ipsilateral subscapularis control specimens or cadaveric supraspinatus controls (Table 2). Patients with patellar tendinopathy were often in their 30s, while patients with Achilles tendinopathy tended to be in their 40s and patients with rotator cuff tendinopathy in their 50s and 60s (Table 2 and S1–S3) Tables. Across anatomical locations, cadaveric controls tended to span a wider age range and were often older than...
the patients. Both men and women were included in 71% of the studies, but relatively few considered potential sex-related differences[45, 46, 72, 73, 84–86, 103].

Differential gene expression and protein representation

Across anatomical locations, the majority of studies (40 of 54 studies) focused on collagens, MMPs, TIMPs, and/or proinflammatory cytokines. The content of the following proteins tended to be increased in tendinopathy: aggrecan (3 positive studies out of 4), fibronectin (3 of 3 studies), tenascin C (TNC) (2 of 3 studies), cyclooxygenase (COX)-2 (3 of 3 studies), collagen I (11 of 15 studies) and III (13 of 14 studies), MMP-1 (6 of 12 studies), -9 (7 of 7 studies), and
| First author, year | Patient samples | Control samples | Method | Up | Down | No difference | Comment | Quality Score |
|--------------------|-----------------|-----------------|--------|----|------|---------------|---------|---------------|
| **Bank, 1999** [36] | Peroperative, ssp, degeneration, n = 10, n.r. (55–80) | Cadavers, ssp, normal, n = 39, n.r. (11–96) | Proteins* | - | Collagen | - | Results from crosslink and pentosidine (AGE) analysis are not included in this table | 71 |
| **Benson, 2009** [37] | II: Peroperative, ssp, impingement, n = 9, n.r. (39–53) | I: Peroperative, ssc, normal from surgery for instability, n = 3, 19.7 (17–23) | Proteins | HIF-1α | - | - | Samples were divided into groups according to macroscopic appearance | 69 |
| **Chaudhury, 2011** [38] | Peroperative, rc, tear, n = 92, 65.7 (45–89) | Peroperative, ssp, normal from other surgery, n = 11, 58 (46–79) | Proteins** | Elastin | Collagen I, Collagen II, Collagen III | Decorin | Samples were subdivided according to tear size | 62 |
| **Hamada, 1997** [39] | I: Peroperative, ssp, full thickness tear, n = 18, 56.7 (36–70) | III: Peroperative, ssp, normal from trauma surgery, n = 4, 41.8 (19–77) | Transcripts | α1-procollagen | - | - | Quantification based on number of label-positive cells in randomly selected areas | 65 |
| **Joseph, 2009** [40] | Peroperative lhb intraarticular portion, rotator cuff or biceps tendinopathy, n = 11, n.r. (36–60) | Peroperative, lhb extraarticular portion from same patient | Proteins | Collagen III, MMP-1, MMP-3 | - | MMP-2, MMP-13, IGF | Correlation found between collagen type III and MMPs | 83 |
| **Lakemeier, 2010** [41] | Peroperative, ssp, full thickness tear | Proteins | Quantification based on number of label-positive cells in relation to total number of cells | 77 |
| **Lakemeier, 2011** [42] | Thickness tear: | | | Patte classification refers to cuff tear retraction in the frontal plane: | |

(Continued)
| First author, year | Patient samples | Control samples | Method | Up | Down | No difference | Comment | Quality Score |
|-------------------|----------------|---------------|--------|----|------|---------------|---------|---------------|
| III: Patte grade 2, n = 10, 65 | MMP-1, MMP-9, HIF-1α, VEGF | - | - | MMP-9 | - | 1: Proximal stump close to bony insertion, 2: proximal stump at the level of the humeral head, 3: proximal stump at glenoid level | Quantification based on number of label-positive cells in relation to total number of cells | 77 |
| II | - | - | MMP-9 | - | - | |
| IV: Patte grade 3, n = 17, 69 | MMP-1, MMP-9, HIF-1α, VEGF | - | - | MMP-9 | - | |
| II | MMP-9 | - | - | |
| III | - | - | MMP-9 | - | |
| Lakemeier, 2010[43] | II: Peroperative, lhb, partial thickness tear, n = 48, 61 | MMP-1, MMP-9, VEGF | I: Peroperative, lhb, normal from trauma surgery, n = 8, 56 (37–69) | MMP-1, MMP-9 | - | - | |
| Lakemeier, 2010[44] | MMP-3 | II, IV | - | MMP-1, MMP-3 | - | - | |
| III: Peroperative, lhb, full thickness tear, n = 42, 67 | MMP-1, MMP-9, VEGF | II, III | - | - | MMP-1, MMP-3, VEGF | |
| Lo, 2004[45] | Peroperative, rc, full thickness tear, n = 10, 59.2 ±4.4 (n.r.) | MMP-13 | Cadavers, rc, normal, n = 6, 74±7 (n.r.) | MMP-3, TIMP-2, TIMP-3, TIMP-4 | MMP-1, MMP-8, MMP-10, TIMP-1 | RT-PCR normalised to GADPH | 83 |
| Lo, 2005[46] | - | MMP-13 | Cadavers, rc, normal, n = 6, 74±7 (n.r.) | Decorin | Collagen II, biglycan | Results on bursal tissue are not included in this table. RT-PCR normalised to β-actin | 79 |
| Lundgreen, 2011[47] | Peroperative, ssp, full thickness tear, n = 15, 57.7 ±7.3 (n.r.) | Peroperative, ssc, normal from arthroscopic labral repair, n = 10, 43.9 (32–51) | HDAC1, MDM4, PPM1D, NF-κB | - | - | Gene expression analyses were performed on a subset of the torn ssp and reference ssc | 73 |
| | - | p53, ki67 | - | - | RT-PCR normalisation gene n.r. | |
| Millar, 2008[18] | I: Peroperative, ssp tear, n = 17, 57 (39–76) | MIF, IL-18, IL-6, Cap-3, Cap-8, HSP-70, HSP-27 | Ia: Peroperative, ssc, normal | - | - | Results from a rat study | 85 |
| Millar, 2009[48] | - | RT-PCR normalised to β-actin | scripts | not included in this table. RT-PCR normalised to β-actin | |

(Continued)
| First author, year | Patient samples | Control samples | Method | Up | Down | No difference | Comment | Quality Score |
|--------------------|-----------------|-----------------|--------|----|------|--------------|---------|--------------|
| I                  | II: Peroperative, ssc, normal from surgery for instability, n = 10, 35 (20–41) | Transcripts | MIF, IL-18, IL-15, IL-6, Cap-3, Cap-8, HSP-70, HSP-27 | TNFα, cFlip | - |
| I, Ia              | II              | Transcripts | MIF, IL-18, IL-15, IL-6, Cap-3, Cap-8, HSP-70, HSP-27 | - | - |
| I, Ia              | II              | Proteins     | MIF, IL-18, IL-15, IL-6, Cap-3, Cap-8, HSP-70, HSP-27, TNFα | cFlip | - |
| Millar, 2012 [17]  | I: Peroperative, ssp tear, n = 15, 55 (38–70) | Probes     | - | HIF-1α, clusterin, Bcl-2 | VEGF | Results from an in vitro hypoxia study are not included in this table | 81 |
| Ia                 | II: Peroperative, ssc, normal from the same patient | Proteins | - | HIF-1α, clusterin, Bcl-2 | VEGF | Results from a mouse study are not included in this table | 54 |
| I, II              | Ia              | Proteins     | - | HIF-1α, clusterin, Bcl-2 | VEGF | Results from a mouse study are not included in this table | 75 |
| Oliva, 2009 [49]   | Peroperative, ssp tear, n = 5, 60±1 (n.r.) | Cadaver, ssp, normal, n = 5, 65±1 (n.r.) | Transcripts | - | TG2 | TG1, FXIII | - |
| Riley, 1994 [50]   | II: Peroperative, ssp tear, n = 26, 59.6 (38–80) | I: Cadaver, ssp, normal, n = 60, 57.7 (11–95) | Proteins | Collagen III | (Total collagen) | - | RT-PCR normalisation gene n.r. | 75 |
| III: Peroperative, ssc tear, n = 8, 73.4 (68–80) | Ia: Cadaver, common biceps, n = 24, 53.6 (12–83) | Proteins | FXIII | TG2 | - |
| Riley, 2002 [51]   | Peroperative, rc, partial/ full thickness tear, n = 10, n. r. (65–80) | I: Cadaver, biceps, normal, n = 24, n. r. (18–89) | Proteins | MMP-1 | - | MMP-2, MMP-3 | Number of samples per patient/cadaver not specified | 79 |
| II: Cadaver, ssp, normal, n = 29, n. r. (10–96) | Proteins | MMP-1, denatured collagen | MMP-2, MMP-3 | - | - |
| Qi, 2012 [58]      | Peroperative, biceps, rotator cuff repair, n = 11, n. r. (27–67) | Peroperative, flexor radialis carpi, normal, n = 5, n. r. (27–67) | Transcripts | Tenomodulin isoform II | - | Tenomodulin isoform I, tenomodulin isoform III | qPCR normalised to 18s rRNA. Results from cell studies are not included in this table | 86 |
| First author, year | Patient samples | Control samples | Method | Up | Down | No difference | Comment | Quality |
|-------------------|-----------------|----------------|--------|----|------|---------------|---------|---------|
| Shindle, 2011[52] | Ia: Peroperative, ssp, full thickness tear, n = 24, 62.4 ±2.0 (n.r.) | Ila: Peroperative, ssp, partial thickness tear, n = 16, 56.3±1.7 (n.r.) | Transcripts | MMP-9, MMP-13, COX-2, (COL1A1) | iNOS | COL3A1, II-1β, IL-6, TNFα, VEGF, MMP-1, TIMP-1, SMA, biglycan | Results on synovial and bursal specimens are not included in this table | 92 |
|                   | Ilb: Peroperative, ssc, normal from same patient | | | | | | |
| Shirachi, 2011[53] | Peroperative, rc, full thickness tear, n = 12, 58.2 (47–68) | Cadaver, rc, normal, n = 5, 66.2 (57–76) | Transcripts | Collagen I, Collagen III | - | - | Only 5 tear samples and 2 control samples were subjected to protein analysis | 75 |
| Singaraju, 2008[54] | Peroperative, lhb, biceps tendinopathy, n = 6, 51 (44–60) | Cadaver, lhb, normal, n = 6, 76 (42–81) | Proteins | Collagen I, Collagen III | - | - | RT-PCR normalised to β-actin | 31 |
| Tillander, 2002[55] | II: Peroperative, ssp, impingement, n = 16, 51 (30–61) | I: Peroperative, ssc, normal from instability patients, n = 9, 28 (20–37) | Proteins | Fibronectin, (MMP-1) | - | - | MMP-1 was only found in few patients in groups II and III | 69 |
|                   | III: Peroperative, ssp tear, n = 7, 57 (41–73) | | | (MMP-1) | Fibronectin | - | |
| Tomonaga, 2000[56] | Peroperative, ssp, full thickness tear, n = 28, 55.9 (36–77) and ssp, partial thickness tear, n = 14, 54.6 (26–72) | I: Peroperative, ssp normal (other surgery), n = 4, 40.8 (19–73) | Transcripts | Procollagen α1 type III | - | - | Results on synovial specimens are not included in this table | 46 |
|                   | II: Apparent trauma: 25 of the above 42 patients | | | Procollagen α1 type III | - | - | |
|                   | III: No apparent trauma: 17 of the above 42 patients | | | Procollagen α1 type III | - | - | |
| Wang, 2001[57]    | Peroperative, degenerative ssp, n = 13(?), n.r. (n.r.) | Peroperative, ssc, normal from same patient | Transcripts | PRDX5 | - | - | RT-PCR normalised to β-actin | 65 |
Studies examining biceps tendon samples are included in this table. None of the studies that quantified proteins used proteomics technologies. Two authors in same row indicate that the same patient and control populations were used in the two studies; () = non-significant trend.

Abbreviations: bb = biceps brachii tendon, bcl = B cell lymphoma, cap = caspase, CB1R = cannabinoid receptor type 1, CCL = chemokine ligand, CGRP = calcitonin gene related protein, COX = cyclooxygenase, FXIII = factor XIII, GADPH = glyceraldehyde 3-phosphate, HDAC = histone deacetylase, HIF-1α = hypoxia inducible factor-1α, HSP = heat shock protein, IGF = insulin-like growth factor, IL = interleukin, iNOS = inducible nitric oxide synthase, lhb = long head of biceps tendon, MDM4 = double minute 4 protein, MIF = macrophage migration inhibitory factor, MMP = matrix metalloproteinase, NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells, n.r. = not reported, p53 = protein 53, PPM1D = protein phosphatase 1D, PRDX = peroxiredoxin, rc = rotator cuff tendon, SMA = smooth muscle actin, SP = substance P, ssc = subscapularis tendon, ssp = supraspinatus tendon, TG = transglutaminase, TIMP = tissue inhibitor of metalloproteinases, TNF-α = tumor necrosis factor-α, VEGF = vascular endothelial growth factor.

* Reversed-phase high performance liquid chromatography.

** Fourier transform spectroscopy.
-13 (4 of 7 studies), TIMP-1 (4 of 7 studies), and vascular endothelial growth factor (VEGF) (4 of 7 studies). For MMP-2, 5 of 11 studies found increased levels relative to controls, and for biglycan and versican, this was the case for 2 of 6 studies and 3 of 8 studies, respectively; the remainder did not observe any difference, except that one study found decreased levels of three versican variants in painful and ruptured Achilles tendons[61]. Meanwhile, the content of MMP-3 (10 of 12 studies) tended to be decreased, and there were some indications that this was also the case for TIMP-2 (2 of 6 studies), -3 (2 of 5 studies), and -4 (2 of 4 studies). Results with respect to a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), a disintegrin and metalloproteinase (ADAM), and proinflammatory cytokines were inconsistent, or few studies reported their regulation/expression. The direction of change of the most frequently examined transcripts and proteins was similar across tendon type. This was particularly evident for collagen I and-III, MMP-3, -9, and -13, and VEGF, which were examined in all four tendon groups. In general, each study reported on only a few selected transcripts and/or proteins.

Particularly with regard to the rotator cuff, there was a high degree of heterogeneity between studies with respect to the examined transcripts and proteins, and few studies compared specimens from degenerated and torn supraspinatus tendons. In one study, levels of BNip3 positive cells were higher in samples from patients with tears compared with samples from patients with subacromial impingement syndrome, combined with a rise in ‘apoptotic index’[104]. This might indicate that the pathological features of subacromial impingement syndrome are exacerbated in tears, in support of the theory of progressive failure of the rotator cuff. A group of similar studies[42–44], in which supraspinatus or long head of biceps tendon samples from torn rotator cuffs were divided in groups according to tear size, indicated that the expression/representation of HIF-1α[43], VEGF[43], and MMP-9[41, 42] was enhanced as rotator cuff pathology worsened. Two studies found similar correlations between increasing expression/representation of VEGF[44], MMP-1, and -9[41] and increasing extent of a full-thickness rotator cuff tear, but these findings were not statistically significant. On the other hand, two studies of apoptosis and cytokines in torn supraspinatus tendons showed no correlation between apoptotic[18] and cytokine gene expression[48] and tear size/histological grade, and a similar study even found an inverse correlation between tear size and apoptotic markers[17].

**Publication bias**

To examine the possibility of publication bias, we plotted the direction of change of MMP-3 content in relation to study size (Fig 2). Since the content of MMP-3 tended to be decreased in tendinopathy, the plot would indicate publication bias if smaller studies tended to report a decrease of MMP-3 in tendinopathy less often than larger studies did. Study size varied from 5 to
116 patient samples; only two studies had a size of >50. Two studies reported both an increase and a decrease in MMP-3 for different comparisons; in these cases, we chose to report only the result from the comparison between patient and control samples[41] and prioritised samples taken from the same anatomical location[51]. One study showed only a borderline decrease in MMP-3[78], but we presented the result as a decrease in the figure. Five studies had a sample size ≤20, of which four reported a lower expression/representation of MMP-3 (80%). Seven studies had sample a size >20, of which six reported a lower expression/representation of MMP-3 (86%). Thus, similar results were reported in small and large studies.

Discussion

This systematic review was performed to examine the literature on differential gene expression and protein composition in human tendinopathy including tears, as well as to provide insights into the potential of proteomics. Across anatomical regions, several gene transcripts and proteins were differentially expressed/represented in samples from patients with tendinopathy compared to control samples. The most consistent findings were an increase in collagens I and III, MMP-1, -9, -13, TIMP-1, and VEGF, and a decrease in MMP-3. With regard to the rotator cuff, it was not possible to determine, whether specific changes were characteristic of tears as compared with tendinopathy. Our most important result was that we were unable to identify any proteomics studies that fulfilled our inclusion criteria.

Proteomics has gained interest in studies of other musculoskeletal disorders[27–31]. To search specifically for proteomics studies on musculoskeletal topics, we developed an additional specific search string, which retrieved these other studies (S3 Appendix). Using this string, we identified five studies, which had not already been captured by the comprehensive searches, but still none that fulfilled our inclusion criteria. A recent review (which we return to below) did not
include studies that we missed\cite{105}. Thus, we find it unlikely that we missed important proteomics studies of tendinopathy. Publication bias and bias due to selective reporting of findings within a study may have influenced our results. Our plot of the findings for MMP-3 in relation to sample size (Fig 2) was not a very sensitive method of detection since almost all the depicted studies were small. Nonetheless reassuringly, we did not reveal any indication of such bias.

The transition from healthy tendon to tendinopathy must be gradual and it is difficult to draw a clear line between pathological and control specimens. Control specimens in terms of bursal and subscapularis tissues as well as the intraarticular portion of the long head of the biceps tendon from joints with supraspinatus tendinopathy including tears often showed signs of degeneration\cite{40, 52, 106, 107}, which suggests a global affection of different subacromial soft tissues. For example, degenerative changes were found in subscapularis tendons from patients with supraspinatus tears, even though they appeared normal on preoperative magnetic resonance imaging\cite{52}. Using paired subscapularis controls to analyse differential protein composition may therefore underestimate actual differences from normal. Furthermore, the use of subscapularis controls or tendons from other anatomical locations may add bias due to normal, functional variations in tendon composition\cite{108–111}. Strictly standardised biopsy procedures are probably important to ensure reproducibility and account for regional variations in protein composition within a tendon. Moreover, human tendon specimens often represent late stages of disease, and unless time-sequential tissue samples are obtained, it is impossible to determine, whether observed changes preceded or succeeded a rupture. The use of cadaveric controls also entails problems; post-mortem changes may interfere with the results and, according to our findings, the cadaveric controls were often older or spanned a wider age range than the patients. The prevalence of rotator cuff tendinopathy increases with age\cite{112, 113} and studies of cadaveric rotator cuff tendons have revealed that the proportion of samples showing histological signs of degeneration increases with age even in undiagnosed cadavers\cite{114, 115}. As a minimum, cadaveric controls should therefore be comparable to the patients with respect to age.

In the following, we interpret our results in view of contributory evidence from animal and cell culture studies as well as other research areas. We also discuss our findings and interpretations against a recent review of histological and molecular changes in rotator cuff disease\cite{105}. Apart from methodological differences regarding searching and critical appraisal of the literature, the just-mentioned review differed from ours in that it was restricted to rotator cuff tendons, included animal and in vitro studies, and did not focus on proteomics research. Based on an outline of general shortcomings in studies of transcripts and proteins using probes, primers, and antibodies, we then evaluate the potential of proteomics in tendon research.

### Collagens

An increased expression of collagen III was related to tendinopathy including tears in all\cite{40, 46, 53, 64, 66, 69, 70, 73, 74, 79, 86, 116} but 2\cite{33, 38} of 45 included studies, which examined this protein. This change was evident both with respect to gene expression, i.e. transcripts (mRNA), and with respect to protein representation. The ratio of collagen I to collagen III was often decreased in tendinopathic specimens. A decreased ratio of collagen I to collagen III may be interpreted as a sign of tissue remodelling\cite{110} and has previously been associated with decreased mechanical stability and a propensity for inguinal hernia recurrence after surgical repair\cite{117}. Collagen III is normally synthesised in early stages of wound healing and is considered to be an immature form of collagen I\cite{110, 118}. Collagen III fibrils have a thinner diameter, and are more elastic and less organised than collagen I.
In healthy tendons, advanced glycation end products (AGEs) are formed in an irreversible reaction and these products therefore tend to accumulate in long-lived proteins like collagen [36, 119, 120]. After 50 years of age, even normal supraspinatus tissue shows signs of tissue remodelling in the form of decreased levels of pentosidine (a non-protein biomarker for AGEs—low levels of pentosidine indicate high contents of AGEs). In tendinopathic and ruptured tendons this remodelling process appears to be accelerated[33, 36, 72]. As a result, pathological supraspinatus tendons appear to be biologically younger than healthy supraspinatus tendons[36]. This may indicate an up regulated tissue turnover in tendinopathy, consistent with the increase in collagen III. The recent review[105] also suggested this theory of an up regulated tissue turnover in degenerated tendons resulting in formation of a mechanically less stable matrix.

Matrix metalloproteinases

MMPs have been implicated in the pathogenesis of rotator cuff tendinopathy[5, 105, 121]. MMPs are able to degrade all kinds of ECM proteins, function as regulators of ECM homeostasis, and are key players in tendon healing and remodelling[5, 121]. They may be involved in the mobilisation of growth factors and cytokines through cleavage of cytokine-binding proteins[122]. According to our review, an increase of MMP-1 (collagenase-1), -9 (gelatinase B), and -13 (collagenase-2), and a decrease in MMP-3 (stromelysin-1) were frequent findings in pathological tendon specimens, along with a tendency towards an increase of MMP-2 (gelatinase A). Similar results were reported in the recent review[105]. This might indicate a shift in metabolism towards matrix degradation, which corresponds well with the observed decrease in the ratio of collagen I to collagen III, and decreased pentosidine levels. MMP-3 is a proteolytic enzyme believed to have regulatory functions in the ECM [123–125] and it is thought to play a part in the regulation of connective tissue remodelling, as it acts as an activator of other MMPs [5]. Interestingly, polymorphisms within the MMP-3 gene have been associated with anterior cruciate ligament ruptures[16] and Achilles tendinopathy[15].

Proteoglycans and glycoproteins

There is a tendency towards an increase in proteoglycans as well as a well-established increase in glycosaminoglycan (GAG) (polysaccharide) content in tendinopathy[73, 126]. This tendency towards a fibrocartilaginous tissue type characterised by increases in the large proteoglycans biglycan and aggrecan and a decrease in decorin was also observed in the recent review[105]. GAGs are able to bind water molecules, and this may account for tendon swelling in tendinopathy. Increases in tendon proteoglycans are often interpreted as a response to compressive loading[62, 127, 128]. Thus, differences in the mechanical environment at the site of biopsy may in part explain the differences in results that we observed between studies. TNC is an elastic glycoprotein, which is often up regulated in response to compressive[129, 130] or tensional [131] loading. Furthermore, TNC is believed to be involved healing processes as well as in the tendon’s adaptation to mechanical stress[129, 132], possibly by providing elasticity to the tendinous tissues[133, 134]. In vitro studies suggest that TNC may also induce inflammatory mediators and matrix degradation in cartilage from osteoarthritic joints[135].

Inflammation and degeneration

In recent reviews, it has been suggested that inflammation and degeneration in tendinopathy are not mutually exclusive, but are instead closely interconnected[1, 21, 136, 137]. The inflammatory theory has often been disregarded due to a lack of evidence of inflammatory cell infiltrates in human tendinopathic specimens, but recently, cytokines related to inflammation have
been found\[4, 48, 52, 65, 85\]. Cytokines are able to influence a wide array of ECM components. In vitro studies of human tenocytes have suggested that tendon contents of several cytokines and neuropeptides may vary in a loading-dependent manner\[105, 138–141\]. Mediators of neurogenic inflammation—i.e., inflammation arising from the release of neuropeptides from afferent neurons\[142]\—including substance P\[143, 144\], calcitonin gene-related peptide (CGRP) \[145\], glutamate\[81\], and the proangiogenic cytokine, VEGF\[43, 44, 71, 82\], have also been associated with tendinopathy. Inflammation may persist in the early stages of tendinopathy and initiate a cascade of catabolic events in the tendon. In fact, a close-knit relationship seems to exist between several pro-inflammatory cytokines and MMPs; for example, in vitro studies have recently shown that interleukin(IL)-1β can induce COX-2, MMP-1, -9, and -13, ADAMTS-4, IL-6 and IL-1β in human tendon cells\[146\], and a strong correlation has been found between the inflammatory cytokine IL-1β and MMP-9\[52\]. Several cytokines and growth factors play an important role in tendon healing\[147–149\], and degenerated and ruptured supraspinatus tendons share many biochemical characteristics of wound healing\[118\]. Cytokines and growth factors are normally increased during wound healing and as mentioned above several may act as proinflammatory mediators. An increase in numerous cytokines and growth factors was also found in the recent review, and the up regulation of proinflammatory cytokines was suggested to result either from ongoing healing or from an imbalance between anabolic and catabolic tendon processes\[105\]. In our review, this was reflected by differential expression/representation of various matrix-degrading enzymes (MMPs), collagens, and other structural matrix proteins.

**Rotator cuff tendinopathy versus other tendinopathies**

We included studies on tendons from various anatomical locations under the assumption that the biological processes leading to tendon degeneration are similar in different tendons. On the other hand, tendons from different anatomical locations vary with respect to morphological and mechanical properties depending on their specialised function, and hence, the pathways to degeneration may vary as well. For example, a distinction is often made between spring-like tendons that are subjected to high strain, and positional tendons that are subjected to lower strain\[150\].

**Transition from rotator cuff tendinopathy to development of tears**

It has long been assumed that there exists a continuum between rotator cuff tendinopathy and the development of tears\[151\], and we would expect this to be reflected in the protein profiles of samples from patients representing these conditions. Few of the included studies compared rotator cuff tendinopathy and rotator cuff tears. Several of these studies indicated that changes in tendon gene expression and protein representation were exacerbated with worsening pathology, but findings were inconsistent. It is possible that only certain types of proteins show a pattern of worsening with cuff pathology, or, indeed—as one study of apoptosis in rotator cuff tears suggested\[17\]—that degenerative and inflammatory activity of tendinopathic tendons decreases following rupture.

**Proteomics in tendon tissue research**

Since proteins are functional effectors of most cellular functions, the study of proteins may provide insights into disease processes, including those that are not reflected on an mRNA level (as mentioned in the introduction, there is no direct relationship between mRNA expression and protein levels). Previously, proteomics technologies required relatively large amounts of tissue, and this may have prevented proteomics studies on patient tendon samples. In recent
years, however, novel MS technologies have allowed reliable analyses of low milligram amounts of biopsy material[152].

Proteomics is primarily based on the use of MS, a highly sensitive analytical tool that uses electrical fields to measure the masses of charged molecules[25, 153–156]. However, high-abundance proteins may mask low-abundance proteins. The high amounts of collagen I in tendon tissue pose a significant challenge and collagen depletion prior to analysis may be necessary. Although MS-based proteomics studies may fail to uncover low-abundant proteins, they may provide comprehensive analyses of the overall protein composition in different stages of tendinopathy.

Proteomics technologies offer new ways of looking at diseases and how they progress. In a single specimen, proteomics analyses may identify hundreds of proteins, and so, a major challenge in MS-based proteomics is to sort out important information from overwhelming amounts of data. This is accomplished with help of bioinformatics, an interdisciplinary field that comprises a range of computational tools (e.g. sequence databases and search algorithms) used to analyse biological data and locate proteins and their biological functions.

The field of proteomics is constantly evolving, and use of these techniques to characterise and quantify differences in protein composition in tendinopathic and healthy samples may improve our understanding of biological processes leading to tendinopathy and tendon tears.

Conclusions

In studies based on methods, which only allowed simultaneous quantification of a limited number of prespecified mRNA molecules or proteins, this review found several markers of tissue remodelling to be differentially expressed/represented in human tendinopathy, most notably collagen I and III, MMP-1, -3, -9, and -13, TIMP-1, and VEGF. With regard to the rotator cuff, it was not possible to determine, whether specific changes were characteristic of tears as compared with tendinopathy. We were unable to identify any proteomics studies of tendinopathic or torn tendon samples from humans, which fulfilled our inclusion criteria. Proteomics technologies may be a way to identify protein profiles (including unexpected proteins) that characterise specific tendon disorders or stages of tendinopathy, and thereby enhance our understanding of pathways involved in tendon damage. Thus, our results suggested an untapped potential for proteomics in tendon research.

Supporting Information

S1 Fig. OMICS technologies. The complexity and size of each compartment increase with each step down the pyramid. Adapted from Holmes et al[26]. (TIFF)

S1 Table. Gene expression and protein composition in patellar tendinopathy. None of the studies that quantified proteins used proteomics technologies. Two authors in same row indicate that the same patient and control populations were used in the two studies; () = non-significant trend. (DOCX)

S2 Table. Gene expression and protein composition in Achilles tendinopathy and ruptures. None of the studies that quantified proteins used proteomics technologies. Two authors in same row indicate that the same patient and control populations were used in the two studies; () = non-significant trend, [] = could not be detected in all samples. (DOCX)
S3 Table. Gene expression and protein composition in various tendinopathies. None of the studies that quantified proteins used proteomics technologies. Two authors in same row indicate that the same patient and control populations were used in the two studies; () = non-significant trend.

S1 Appendix. PRISMA Checklist.

S2 Appendix. Search strings used in Embase and Web of Science.

S3 Appendix. Additional specific search string used for specific proteomics search in Medline.

S4 Appendix. Manual for quality scoring in Table 1 adapted from Kmet, Lee, and Cook’s Standard Quality Assessment Criteria for evaluating primary research papers from a variety of fields [34].

S5 Appendix. Reasons for exclusion after full-text reading (n = 48). Information from some of the excluded papers is used in the discussion.

S6 Appendix. Details on quality scoring of included studies. N/A = not applicable.

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Author Contributions

Conceived and designed the experiments: MHJS PF TBH SRD SWS. Performed the experiments: MHJS. Analyzed the data: MHJS. Wrote the paper: MHJS SWS. Interpreted the data: MHJS PF TBH SRD SWS. Revised the article critically for important intellectual content: PF TBH SRD SWS. Approved the final version of the manuscript: MHJS PF TBH SRD SWS.

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