Defining the extracellular matrix in non-cartilage soft-tissues in osteoarthritis: a systematic review

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Aims

Extracellular matrix (ECM) is a critical determinant of tissue mechanobiology, yet remains poorly characterized in joint tissues beyond cartilage in osteoarthritis (OA). This review aimed to define the composition and architecture of non-cartilage soft joint tissue structural ECM in human OA, and to compare the changes observed in humans with those seen in animal models of the disease.

Methods

A systematic search strategy, devised using relevant matrix, tissue, and disease nomenclature, was run through the MEDLINE, Embase, and Scopus databases. Demographic, clinical, and biological data were extracted from eligible studies. Bias analysis was performed.

Results

A total of 161 studies were included, which covered capsule, ligaments, meniscus, skeletal muscle, synovium, and tendon in both humans and animals, and fat pad and intervertebral disc in humans only. These studies covered a wide variety of ECM features, including individual ECM components (i.e. collagens, proteoglycans, and glycoproteins), ECM architecture (i.e. collagen fibre organization and diameter), and viscoelastic properties (i.e. elastic and compressive modulus). Some ECM changes, notably calcification and the loss of collagen fibre organization, have been extensively studied across osteoarthritic tissues. However, most ECM features were only studied by one or a few papers in each tissue. When comparisons were possible, the results from animal experiments largely concurred with those from human studies, although some findings were contradictory.

Conclusion

Changes in ECM composition and architecture occur throughout non-cartilage soft tissues in the osteoarthritic joint, but most of these remain poorly defined due to the low number of studies and lack of healthy comparator groups.

Article focus

- Extracellular matrix (ECM) is a critical determinant of tissue mechanobiology and cell behaviour, but it is poorly described in osteoarthritic joint tissues beyond cartilage.
- The main aim of this systematic review is to consolidate existing data describing the architecture and composition of structural ECM in the synovium, joint capsule, skeletal muscle, tendon, ligament, meniscus, intervertebral disc, and fat pad of osteoarthritic joints.

Key messages

- Our study highlights the global nature of ECM dysregulation across the osteoarthritic joint.
- While some ECM changes, notably calcification and the loss of collagen fibre

organization, have been extensively studied across osteoarthritic tissues, most ECM features were only studied by one or a few papers in each tissue.
- Results from animal studies generally concurred with human studies, but some findings contradicted observations from human studies, highlighting the importance of the choice of animal model and the need for validation from human studies.

Strengths and limitations

- This systematic review consolidates existing knowledge of a poorly defined aspect of osteoarthritis pathophysiology.
- While a wide range of tissues and ECM components have been reported on, the qualitative nature of papers, the lack of control groups, and the paucity of reports on each ECM component means that the depth of knowledge remains poor.

Introduction

Osteoarthritis (OA) is the most common joint disease globally, affecting over 500 million people. OA is typically attributed to mechanically driven joint damage and is characterized by articular cartilage degeneration and subchondral bone remodelling.[1] However, these tissues are not affected in isolation from the wider joint, with pathology in other soft joint tissues contributing to the symptoms and progression of OA.[2,3] Damage to menisci and ligaments disrupts joint biomechanics, while inflammation, fibrosis, and distension of the synovium and joint capsule are associated with joint pain and stiffness.[4-8] Despite significant clinical need and substantial efforts to identify disease-modifying OA drugs, there is no effective way of inhibiting or decelerating OA-related joint damage by targeting cartilage directly. Given the important role of other soft-tissues in joint biomechanics and the release of pro-inflammatory and matrix-degrading mediators into the synovial fluid,[9,10] understanding the biological landscape of the whole joint in OA might provide novel therapeutic strategies and prognostic markers.

Joint tissues are rich in extracellular matrix (ECM), a network of structural and regulatory macromolecules within which cells are embedded.[11] The role of ECM as a major determinant of the biophysical properties of a tissue has clear relevance in a disease such as OA.[12,13] ECM not only provides structure to the tissue, but can also affect cell function through receptor engagement, mechanical cues, and the sequestration of growth factors and cytokines.[14-17] Significant crosstalk occurs between cells and matrix components, such that pathological ECM may exacerbate cellular dysfunction in disease.[16,18] Therefore, ECM composition and architecture cannot be disregarded when attempting to understand OA pathophysiology. However, outside of cartilage, ECM remodelling in OA tissues has received relatively little attention.

Studying OA in the clinical setting is challenging due to the slow and unpredictable nature of the course of the disease. In addition, clinical symptoms often appear late in the disease process, making it difficult to study its onset and early progression. Therefore, many animal models for OA have been developed to overcome these issues and facilitate the development and evaluation of new therapies and diagnostic tools.[19] However, since there is no single "gold standard" animal model that accurately reflects all aspects of human disease, a major challenge is selecting the "right" model for each study.[20]

The main aim of this systematic review is to consolidate existing data describing the architecture and composition of structural ECM in the synovium, joint capsule, skeletal muscle, tendon, ligament, meniscus, intervertebral disc, and fat pad of osteoarthritic joints. The second aim is to define the changes in the architecture and composition of structural ECM in these tissues in animal models of OA, in order to address their ability to replicate human disease pathophysiology.

Methods

Systematic review protocol and registration number

This review was conducted according to a protocol registered on the PROSPERO database (CRD42021231241) and guidelines set out in the PRISMA statement.[21]

Database and search strategy

The search strategy, written by JYM and a medical librarian, can be found in the Supplementary Material. ECM components and architectural features were defined using National Centre for Biotechnology Information Medical Subject Heading terms.[22] Non-cartilage soft joint tissues and disease nomenclature were also specified. The search strategy was validated against relevant papers identified in a preliminary literature search. The search strategy was run on the Ovid MEDLINE, Ovid EMBASE, and Scopus platforms on 30 October 2020 and repeated on 1 October 2021 and 1 June 2023.

Eligibility criteria and screening

Abstracts were de-duplicated in Mendeley Reference Manager (Elsevier B.V., Netherlands) before being imported into the Covidence platform. The remaining studies were screened independently at title/abstract and full-text stages by two reviewers (JYM, IGAR), with conflicts resolves through consensus or a third reviewer (SJBS). Included studies were required to have ≥ three OA participants.

In human studies, eligible patients and controls were aged ≥ 18 years. Non-OA diseases, including inflammatory arthritides and crystalline arthropathies, were excluded. The presence of a valid control group was not a requirement for human studies. However, control groups were included if present and a minimum of three participants were included in this group. Valid control groups included tissues from healthy people or near-healthy tissues, including cadavers, individuals with osteosarcoma, and traumatic joint injuries provided that the comparator tissue was not directly damaged by the trauma.

In contrast to human studies, all animal studies required a control group. Studies that induced OA unilaterally and only used a contralateral control joint were excluded, as non-physiological loading of the contralateral joint induces ECM remodelling.[23,24] Excluded animal models included the genetic deletion of ECM components, the introduction of matrix-degrading enzymes into the joint, surgical damage of a tissue subsequently reported on, and the ovariectomized rat model, as this is more commonly used as a model for osteoporosis.[25,26]

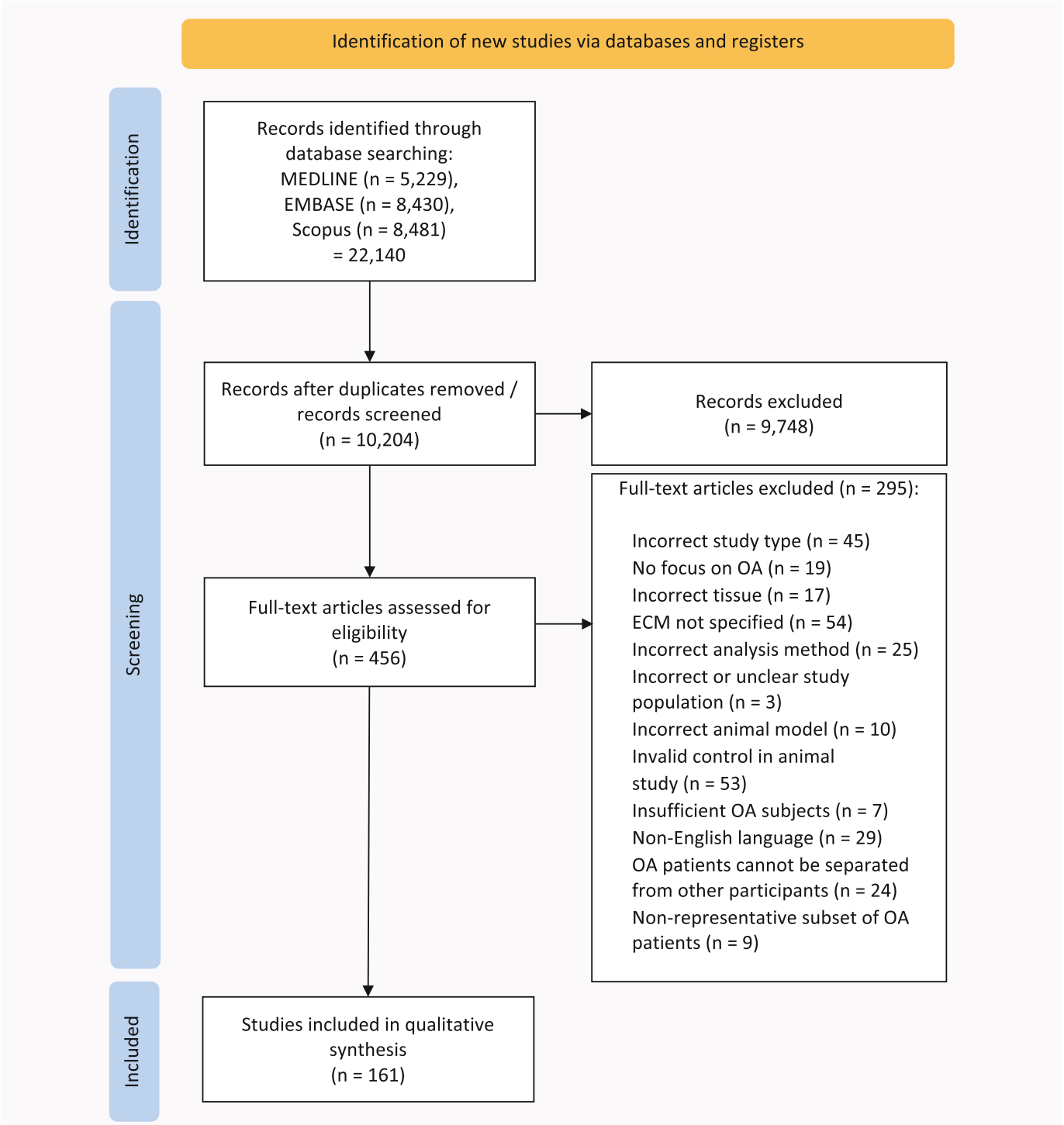

Fig. 1
PRISMA 2022 flow diagram. ECM, extracellular matrix; OA, osteoarthritis.

Regarding outcome measures, included studies evaluated at least one of the following tissues: intervertebral disc, ligament, skeletal muscle, tendon, meniscus, articular capsule, synovium, and fat pad. Papers that only studied these tissues after treatment, including – but not limited to – surgical or drug treatment, or after these tissues were purposely injured to induce the development of OA, were excluded. Papers evaluating non-ECM tissue components (cells, cytokines, matrix-degrading enzymes) were ineligible for inclusion. Given the focus on structural ECM, regulatory matricellular proteins, as well as neoepitopes generated during ECM turnover, were not included. Studies using in vitro or ex vivo culture systems were excluded as the ECM proteins that cells synthesize differ in culture and in vivo. Transcriptomic analyses were excluded as gene expression is a determinant, not a measure, of protein abundance. Finally, only English-language articles were included.

Data extraction and bias analysis

Data were extracted from all included studies by one reviewer (JYM or IGAR) using a standardized extraction form in Microsoft Excel (Microsoft, USA); the extraction was verified

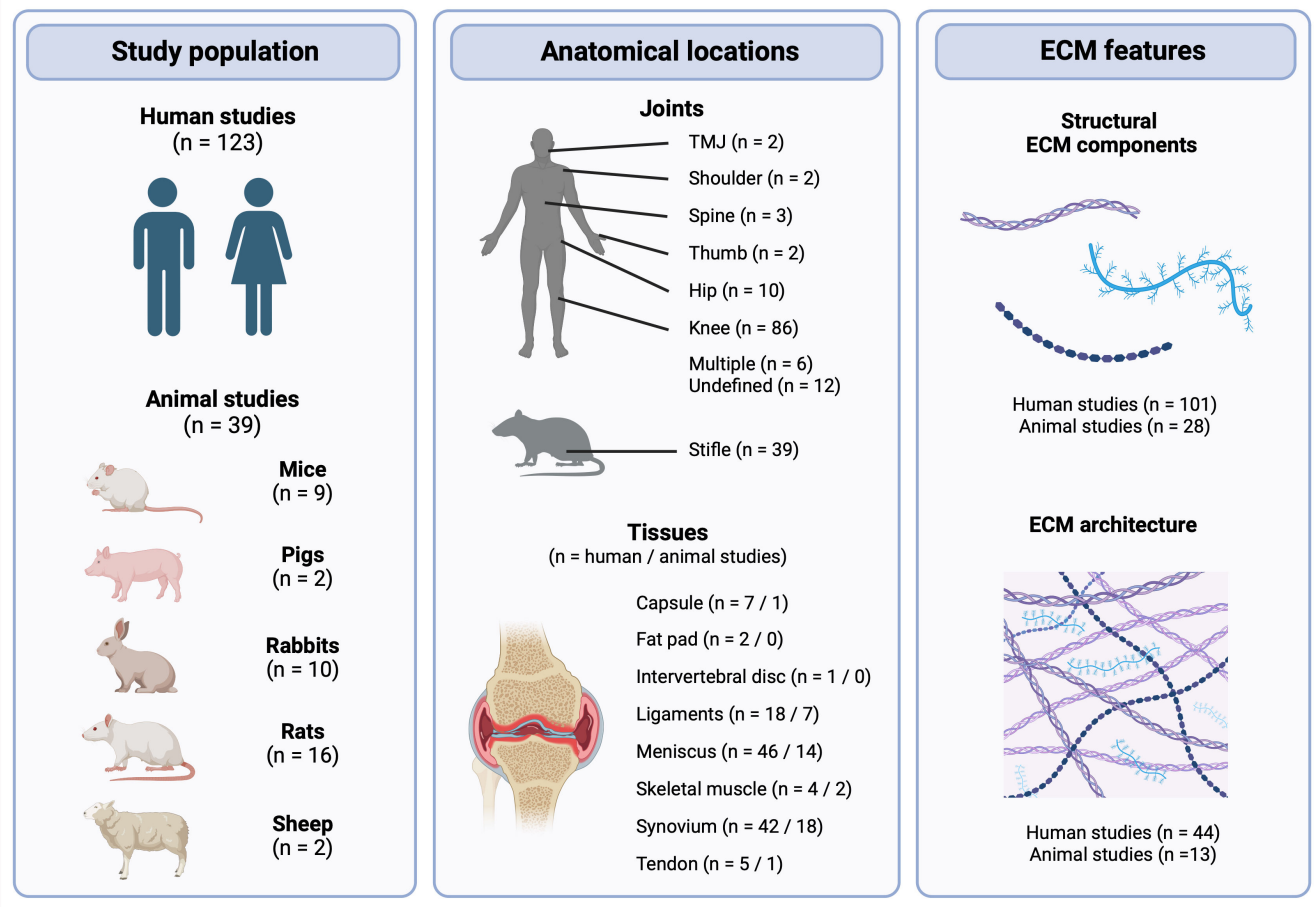

Fig. 2
Schematic overview of the study population, anatomical locations, and extracellular matrix (ECM) features studied in the included studies. One study investigated ECM in both human osteoarthritis (OA) and an animal model of OA. Created with BioRender.com. TMJ, temporomandibular joint.

by the other reviewer (IGAR or JYM). Where there was uncertainty, extraction was performed in duplicate by both reviewers. Number of participants (or animals) in each group was recorded as well as the presence/absence of a control group; if a control group was present, the control population and control tissue were described. For animal studies, the species, strain, and type of OA model were recorded. When available, participant age, sex, BMI, and disease severity were recorded, as were the joint and tissue being studied. Relevant ECM components and architectural features were described; comparisons to control tissues and statistical analysis were noted when applicable. Results were grouped by tissue, followed by ECM feature, and finally the direction of change compared to control (increase, no change, decrease, or no control group present) and presented in Supplementary Table i (human studies) and Supplementary Table ii (animal studies). Due to the large number of different included ECM features, accepted research methods, and accepted measures of effect, a quantitative meta-analysis was not deemed appropriate. Bias analysis was performed by IGAR, with all included studies assessed using the 2015 Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies. The results of the bias analysis can be found in Supplementary Table iii.

Results

Study overview

A total of 22,140 potentially relevant articles were identified by the search strategy (Figure 1). Following the removal of duplicates, 10,204 abstracts were screened. Of the 456 studies assessed for eligibility at full-text screening, 161 met all criteria for inclusion in this review. The characteristics of all included studies are summarized in Supplementary Tables iv and v (human and animal studies, respectively). A schematic overview of the included studies can be found in Figure 2.

Human studies

Most studies investigated meniscus (n = 46) and synovium (n = 42), followed by ligaments (n = 18), capsule (n = 7), tendon (n = 5), skeletal muscle (n = 4), fat pad (n = 2), and intervertebral disc (n = 1) (Supplementary Table i). Studies most commonly investigated the knee joint (n = 86), but papers on hip (n = 10), spine (n = 3), thumb (n = 2), temporomandibular joint (TMJ) (n = 2), and shoulder (n = 2) were also identified. While most studies on synovium, tendon, and capsule focused on the presence/absence and distribution of specific ECM components, a large proportion of the papers on meniscus and ligaments investigated ECM architecture and viscoelastic properties (Supplementary Table i).

Capsule in human OA

Of seven studies which assessed the capsule (hip (n = 3), knee (n = 3), and spine (n = 1)),[27–33] four were published before the year 2000. These studies covered both ECM components and architectural features, but only collagen content was covered by more than one study, with two papers describing increased collagen staining.[28,29] Voelker et al[30] looked at several ECM components, showing an increase in type I collagen and no difference in type III collagen and elastin in OA facet joint capsule compared to cadaver controls.[30] Of note, DiFrancesco et al[27] studied several ECM features (calcification, collagen fibre organization, elastic fibres, and GAG/proteoglycan content) in parallel,[27] providing an overview of hip capsule in OA. Other studies showed decreased collagen fibre organization,[32] the presence of several GAGs,[33] and an increase in collagen cross-links in OA.[31]

Fat pad in human OA

Two studies were identified for infrapatellar fat pad.[34,35] Grevenstein et al[35] found no change in cartilage oligomeric matrix protein (COMP) content between OA and control fat pads,[35] while Belluzzi et al[34] showed that the osteoarthritic fat pad contains less collagen type I and III than controls.

Intervertebral disc in human OA

One study was identified for intervertebral disc. Cheng et al[36] showed an increase in calcification with increasing OA grade in intervertebral discs.

Ligaments in human OA

Of the 18 studies on ligaments, 14 focused on anterior cruciate ligament (ACL) and/or posterior cruciate ligament (PCL) of the knee.[37–50] Two studies looked at ligaments in the thumb (palmar beak ligament,[51] volar anterior oblique (AOL), and dorsoradial (DRL)[52]), while two other studies investigated ligaments in the spine (transverse ligament[53] and the ligamentum flavum).[30] Studies mostly focused on collagen fibre organization, which generally decreased in OA compared to control.[42–44] Studies without controls also reported disorganized and irregular collagen fibre organization in OA ligaments. Other identified studies confirmed the presence of collagens I, II, and III, but found no change in overall collagen content compared to control. In contrast, calcification and proteoglycan content appear to increase in OA.

Meniscus in human OA

Studies on human meniscus (n = 46) covered a wide range of ECM components, architectural changes, and viscoelastic properties.[54–99] Most studies concur on an increase in calcification and proteoglycan content, and consistently show a decrease in collagen fibre diameter and organization. The presence or change in many other ECM components has been studied, including aggrecan, biglycan, cartilage intermediate layer protein, collagens and collagen cross-links, COMP, decorin, fibromodulin, glycosaminoglycan (GAG) components, hydroxyproline, keratocan, lubricin, and lumican. Notably, three out of four proteomics studies included in this systematic review evaluated human OA meniscus, identifying a range of ECM and ECM-associated proteins.[97–99] Two of these studies (Folkesson et al[97] and Roller et al[98]) also analyzed control samples and found several proteins to be changed in OA compared to control tissue. For example, both studies report an increase in type VI α 1 collagen and type VI α 2 collagen in OA, and Folkesson et al[97] found a change in protein abundance in several small leucin-rich proteoglycans, such as an increase in lumican and decrease in decorin, an increase in the proteoglycans aggrecan and versican, and a decrease in type III and V collagens.[97,98] Finally, the results on viscoelastic properties are conflicting: while some studies show an increase in elastic modulus[89] and instantaneous modulus,[90] another study showed a decrease in these parameters.[61]

Skeletal muscle in human OA

All four studies on human skeletal muscle studied the ECM components in the vastus medialis or vastus lateralis of the quadriceps muscle.[100–103] These studies demonstrated the presence[103] or increase[102] in type I, III, and IV collagens compared to control. In addition, these studies show the presence of calcification and laminin,[100,102] and an increase in collagen and GAG content.[101]

Synovium in human OA

Synovial tissue was studied in several joints, including the knee (n = 18),[94,104–120] hip (n = 5),[121–125] both knee and hip (n = 6),[126–131] TMJ (n = 2),[132,133] or an unspecified joint (n = 12).[130,134–144] The ECM components most often studied in human synovium were collagens, fibronectins, and laminins. Other ECM features covered by the included studies are aggrecan, calcification, collagen content, collagen fibre organization, collagen cross-links, COMP, elastin, fibromodulin, GAG components, latent transforming growth factor (TGF)-β-binding protein 1, lumican, reticulin, and vitronectin. While the presence and tissue distribution of these components has been clearly shown by several studies, the changes between OA and normal tissue remain unclear, with most studies lacking healthy control groups; instead, OA is often the comparator group in studies investigating rheumatoid arthritis (RA). This includes the identified proteomics study, which compared the OA and RA synovium. They found that several ECM proteins, including type 2 α 1 collagen, versican, and cartilage intermediate layer protein 1 were higher in OA than RA synovium.[143]

Tendon in human OA

Human tendon studies covered a range of different tendons across the body, including Achilles, (long head of) biceps, subscapularis, gluteus medius, and internal obturator.[145–149] Discordant results between studies of anatomically distinct tendons are unsurprising, but disagreement was also seen for two studies on biceps tendon. For example, GAG/proteoglycan content was increased in the long head of biceps and internal obturator tendon,[145,148] unchanged in another study on biceps tendon and subscapularis tendon,[146] and decreased in gluteus medius tendon in OA compared to control.[149] Similarly, increased calcification was seen in obturator tendon,[145] while there was no difference in subscapularis, and a decrease in biceps tendon.[146] In terms of architecture, three out of four studies reporting on collagen fibre organization report a decrease in organization,[145,146,149] while the last reported no difference compared to control.[148] An increase in collagen fibre diameter was found in internal obturator and biceps tendon,[145,146] while no difference was seen in subscapularis and

gluteus medius tendons.[146,149] Finally, no difference was found in the percentage area stained for type I and II collagen and decorin.[148]

Animal studies

Animal studies followed a similar pattern as human studies regarding the most studied tissues: synovium (n = 18), meniscus (n = 14), ligament (n = 7), skeletal muscle (n = 2), tendon (n = 1), and capsule (n = 1) (Supplementary Table ii). A broad range of species, strains, and models were used, all looking at the stifle joint of these animals. Overall, these studies generally found increases in ECM components such as collagen and disrupted ECM architecture, including a decrease in collagen fibre organization in most tissues (Supplementary Table ii). Viscoelastic properties were mainly studied in meniscus, where the elastic and instantaneous modulus tended to decrease.

Capsule in animal models of OA

Only one study was identified on capsule. Loeser et al[150] studied capsule in the DMM model in C57BL/6 mice.[150] Type III collagen was found to be diffusely expressed in OA capsule, predominantly in vascular endothelium. Interestingly, this study also assessed the meniscus, ligament, and synovium, taking a whole-joint approach to OA; they report a diffuse distribution of type III collagen similar to capsule in ligaments and synovium, while there was a pericellular distribution in meniscus.

Ligament in animal models of OA

Ligaments were studied in OA models in mice (n = 4),[150–153] rabbits (n = 2),[154,155] and sheep (n = 2).[156,157] A decrease in collagen fibre organization was reported by two studies.[155,157] While one study reported an increase in GAG staining using toluidine blue in ACL of STR/ort mice,[151] another showed a decrease in Raman spectroscopy peaks related to GAG content in MCL/LCL of ACL transection (ACLT) rabbits.[154] All other reported ECM features were only present in one study. These features include calcification, mineralization, collagen content, types II and III collagen, collagen cross-links, collagen fibre diameter, and mechanical strength.

Meniscus in animal models of OA

ECM changes in meniscus in animal models of OA were investigated by six studies using mouse models,[150,151,158–161] five studies using rabbit models,[162–166] one study using a rat model,[167] and two studies using a pig model.[168,169] Overall, these studies show an increase in calcification/mineralization and types I, II, III, and X collagen, and a decrease in collagen fibre organization. Most studies show a decrease in GAG/proteoglycan content and viscoelastic properties in at least parts of the meniscus. In addition, thickening of the collagen fibres and no change in fibromodulin were found.

Skeletal muscle in animal models of OA

Two studies were identified that investigated skeletal muscle. Shi et al[170] studied the elastic modulus in biceps femoris and rectus femoris muscles in an adapted Videman method in rabbits; they report an increase in elastic modulus in OA compared to control.[170] Lee et al[171] investigated the rectus femoris muscle using a monoiodoacetate (MIA) model in rats; they reported a decrease in collagen levels on days 56 and 87 in OA rats compared to the naïve group.[171]

Synovium in animal models of OA

Synovium was investigated in three studies using mouse models,[150,158,172] 13 studies using rat models,[104,173–184] and two studies using rabbit models.[185,186] All studies on calcification, collagen content, and collagen I showed an increase in OA compared to control. However, results on collagen fibre organization and collagen fibre diameter were less clear, with some studies reporting no change, while others reported a decrease in collagen fibre organization and increase in collagen fibre diameter. Other studied features included types III, V, and XIV collagen, COMP, fibromodulin, lubricin, and viscoelastic properties (elastic modulus), which were each reported on by a single study.

Tendon in animal models of OA

Tendon was investigated in one study by McErlain et al[187] using an ACLT model in rats. They found calcification of the patellar tendon to be more common in OA than control animals.[187]

Bias analysis

The risk of bias varied between studies but was generally high (Supplementary Table iii). The potential for confounding bias was common, with many human studies failing to report on the age, sex, and BMI of participants. Frequently, OA diagnoses were stated without reference to the diagnostic criteria used. Most studies failed to report on the blinding of assessors, even when qualitative histological observations were made. Purely qualitative observations were common, although semiquantitative scoring systems were increasingly used in more recent studies. However, many quantitative and semiquantitative differences between healthy and osteoarthritic tissues were not statistically analyzed.

Discussion

Despite OA becoming more widely accepted as a whole joint disease, the role of and the changes to non-cartilage soft joint tissues remain underexplored. This study aimed to collate current knowledge on the structural ECM of these tissues to summarize and highlight gaps in existing knowledge. For instance, tissues such as the joint capsule and fat pad are very poorly defined, perhaps reflecting their perceived importance in OA. Overall, the studies included in this review show that the presence and/or abundance of many structural ECM components changes in disease, within an ECM that becomes less organized with increasing cartilage damage or increasing tissue-specific degeneration scores.

Human studies covered a range of tissues and ECM features, but focused mainly on calcification, the presence and abundance of proteoglycans, and the presence, abundance, fibre diameter, and fibre organization of collagens. While recent studies begin to define the presence and distribution of many ECM components, a frequent absence of well-defined control groups limits our understanding of the changes in disease. Most ECM features are only described by one or a few studies, highlighting the need for studies that cover multiple ECM features. While studies that did look at the same ECM feature mostly agreed, this was not always the case. This

included studies with control groups that investigated the collagen content in meniscus,[54,72] elastic modulus in meniscus,[61,89] chondroitin sulphate in synovium,[119,130] and calcification and GAG/proteoglycan content in tendon,[145,146,148,149] which all contradict each other in terms of the direction of change. The summary and results tables highlight several potential factors for these differences already, including differences in analysis methods, tissue joint origin, and microanatomical area of studied tissue, emphasizing the importance of in-depth reporting of tissue metadata and methods.

Several recent human studies, mostly in ligaments, tendon, and meniscus, have begun to interrogate both compositional and architectural ECM features within a single tissue. Importantly, such studies can begin to dissect the relationship, including causality, between changes in ECM composition, ECM architecture, and viscoelastic properties. For example, studies in the field have shown that calcification of tendon changes its viscoelastic properties,[188] while the mechanical properties of fibril-forming collagens are dependent on covalent cross-linking,[189] and different matrix proteoglycans differ in their effects on cell-mediated collagen reorganization.[190]

Whole tissue proteomics, which can be used to study the ECM composition of a tissue holistically, was performed in four studies: three on meniscus[97–99] and one on synovium.[143] While the study of ECM proteins using proteomic techniques is subject to methodological biases due to their large size, extensive post-translational modification, and insolubility,[191] they are a powerful tool to better understand relative abundance of ECM proteins and overall tissue composition and formulate new research questions. The application of this technique to other osteoarthritic tissues is likely to provide important insights.

In animal models, OA is induced in a range of species using varied surgical techniques and pharmacological interventions, with no animal model truly replicating human disease.[19,192] Joint mechanics, inflammatory responses, and disease chronicity all vary between animal models.[192,193] If ECM remodelling also differs between species and procedures, it can be assumed that not all animal models are equally suited to the study of changes in osteoarthritic ECM. Certain models may be generally more representative of changes seen in human OA, or better suited to the study of particular joint tissues or ECM features. This review covers a range of ECM changes in several different musculoskeletal soft-tissues across different species and models. Although limited animal studies were eligible for inclusion in this review, some changes in ECM features could be compared between human OA and animal models. Generally similar trends could be seen as in humans, including a decrease in collagen fibre organization and an increase in calcification across ligaments, meniscus, and synovium. However, other observations seem to contradict those in humans; for example, the presence and abundance of collagens seemed to decrease in human osteoarthritic menisci, especially with increasing degeneration of the meniscus,[54,73,75] while this is not reflected in data from any of the animal models in this review, which mainly showed increases in collagens in OA menisci.[151,161,163] Therefore, the models used by these studies, namely the mouse STR/ort, rabbit ACLT, and mouse DMM models, respectively, might not be suitable to infer OA-related changes in human menisci. These results emphasize that more studies on ECM changes in non-cartilage soft joint tissues in human OA and animal models must be compared before the validity of the latter can be accurately defined.

Another important point to note is the difference in the ratio of female/male subjects in human studies compared to this ratio in animal studies: while most human studies include a higher ratio of female than male subjects, many animal studies are done exclusively using male animals. The predominance of women in human studies likely reflects disease prevalence; sex-specific differences in pain, inflammation, cartilage volume, and physical difficulty exist in OA,[194] as well as in the presence of risk factors for the incidence of radiological knee OA.[195] The presence of a sex bias in preclinical research is well established, with many fields having a strong male bias during animal studies.[196] Encouragingly, sex-specific differences in animal models of OA are increasingly being addressed and reported on, including differences in the progression of the disease and response to pain.[197–201] This emphasizes the importance of accounting for sex during the interpretation of results from both human and animal research studies to the human OA patient population.

The strength of any systematic review is partly contingent on the quality of included studies. As discussed in the Results section on bias analysis, the methodology of many studies conferred a high risk of bias, resulting in a low confidence in the evidence provided. In basic science studies utilizing human samples, the baseline characteristics and clinical characterization of OA patients are often missing, or lack necessary detail. Clinical background is a particularly important consideration in the context of soft-tissue calcification, given that crystal depositional diseases, such as pseudogout, can drive OA.[202] Patients' clinical background is poorly reported throughout the literature, as is disease severity, despite ECM and other tissue components differing more from the physiological state with OA progression.[42] As clinical information might not always be available for collection due to ethical constraints, making this clear to readers allows findings to be interpreted in the correct clinical context. Although the search strategy covered many non-cartilage soft joint tissues, some tissues, such as the temporomandibular joint disc and acetabular labrum, were not included. In addition, the focus of this review was on structural components of the ECM, which are the elements that are studied most extensively and make up the majority of tissue ECM. However, this does mean that this work does not provide a complete account of all OA ECM, as non-structural matrix elements such as matricellular proteins or neoepitopes have not been reported on. Finally, a limitation of the review process is the data extraction, which was not done by two independent reviewers, but rather extracted by one reviewer and verified by the other reviewer. However, the effect of this is likely limited as a previous study has reported that while extraction by two independent reviewers is preferable, extraction by one reviewer with verification by a second reviewer has limited influence on the conclusions of a systematic review, especially considering a meta-analysis was not performed in the current work.[203]

In the process of consolidating the current literature on this topic, this work highlights several practical and

methodological challenges that have limited progress in the understanding of structural ECM components, architectural features, and viscoelastic properties in non-cartilage soft-tissues in OA. One of these problems is the cross-sectional nature of studies, which is popular in the OA field as tissues are only accessible at the time of joint arthroplasty. Since OA can take decades to progress, the study of end-stage or advanced OA might not be fully informative of the processes that are driving these changes. In addition, the lack of a healthy, or non-OA, comparator group, in combination with the fact that many studies only report qualitative results, vastly reduces the depth of knowledge that can be gained from these studies. Finally, while many screened human and animal studies investigated both cartilage and other soft joint tissues, ECM is often studied exclusively in cartilage, with other features, such as cellularity and inflammatory markers, being the focus in other tissues. This shows that while there is access to both the tissues and the methods to study ECM changes in non-cartilage soft-tissues, the analysis of these tissues is not seen as a priority. However, due to the limited characterization of ECM in these tissues and their unknown contribution to disease development and progression, it is also possible that it remains unclear which ECM feature(s) should be focused on. Structural ECM encompasses a wide range of features that can be investigated with a plethora of different methods. To evaluate the most critical ECM features and applicable methods, studies investigating multiple ECM features in non-cartilage soft-tissues across different stages of disease are required.

Recent studies have started to highlight the importance of ECM as a determinant of tissue architecture and cell behaviour in disease. For example, a recent review highlights that the changes in microenvironment in early RA form important extracellular cues that shape the pathogenic cell behaviour during the onset and progression of disease.[204] Therefore, the authors argue that understanding the ECM changes across different tissues in a particular disease might not only be able to help with disease classification and patient stratification, but could also hold promise for the development of treatments that target ECM.[204] These treatments might not only be able to modify pathogenic cell behaviour that could be driving the disease, but also impact on joint stiffness, which is one of the most common symptoms of OA.[205] All in all, more research is needed to unravel the presence and distribution of different ECM components and architectural features in joint tissues in health and in (different stages of) OA, and interplay with tissue-resident and tissue-infiltrating cells. Future research will also help to differentiate between the remodelling process in different joint tissues, which contain unique cell populations and are exposed to different mechanical and inflammatory stimuli in OA. ECM remodelling may also differ between synovial joints, given their varied anatomical locations, mechanical functions, and the presence of joint-specific tissues such as menisci. Potential variation in pathophysiology between OA joints has received little attention, with the predominance of studies on knee OA likely due to high disease prevalence in this joint and tissue being relatively accessible during commonly performed knee arthroplasties. Therefore, the future of this field is both dependent on the thorough investigation of ECM features in non-cartilage soft joint tissues across multiple OA joints and varied stages of disease progression, as well as the rigorous reporting of patient characteristics of all tissue donors.

In conclusion, this systematic review consolidates existing knowledge of a poorly defined aspect of OA pathophysiology. While a wide range of tissues and ECM components have been reported on, the qualitative nature of papers, the lack of control groups, and the paucity of reports on each ECM component means that the depth of knowledge remains poor. Overall, the studies included in this review show that the presence and abundance of many structural ECM components change in OA, and that the ECM architecture becomes more disorganized with increasing cartilage damage or increasing tissue-specific degeneration scores. While results from animal studies generally concurred with human studies, some findings contradicted observations from human studies, highlighting the importance of the choice of animal model and the need for validation in human studies. Given the role of ECM in influencing cell behaviour, further research to elucidate the broad context within which cartilage is damaged in OA will provide more insight into the disease as well as potential treatments.

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Supplementary material

Search strategy for Ovid MEDLINE, Ovid Embase, and Scopus platforms; tables of structural extracellular matrix components and architectural features in non-cartilage soft tissues of human osteoarthritic joints and animal models of osteoarthritis; table of the 2015 OHAT risk of bias analysis of all included studies; and tables of characteristics of the included human and animal studies.

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Data sharing

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. In addition, the raw data from the data extraction process, which were used to populate Supplementary Tables i, ii, iv, and v, are available upon reasonable request from the corresponding author.

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